

Supplementary Online Content

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eTable 1. Conditions for Cohort Inclusion and Exclusion

Inclusion Criteria: Measured during the 365 days prior to index date to 180 days after index date	Reason for Inclusion
At least 1 diagnosis of an SSRI indication:	
Depression	SSRI indication
Obsessive-compulsive disorder	SSRI indication
Post-traumatic stress disorder	SSRI indication
Social anxiety disorder	SSRI indication
Panic disorder	SSRI indication
Generalized anxiety disorder	SSRI indication
Bulimia nervosa	SSRI indication
Exclusion Criteria: Measured during the 365 days prior to index date	Reason for Exclusion
Previous antidepressant use	New users only
Diagnosis of diabetes (type 1 or type 2)	Minimize reverse causation
Gestational diabetes	Minimize reverse causation
Secondary diabetes	Minimize reverse causation
Insulin use	Minimize reverse causation
Antidiabetic medication use	Minimize reverse causation
Pregnancy	Rule out gestational diabetes (related to outcome)
Sickle cell disease	Minimize confounding by underlying disease severity
Cystic fibrosis	Minimize confounding by underlying disease severity
Cancer	Minimize confounding by underlying disease severity
HIV	Minimize confounding by underlying disease severity
Organ transplant	Minimize confounding by underlying disease severity
Dialysis/End stage renal disease (ESRD)	Minimize confounding by underlying disease severity
Respiratory failure	Minimize confounding by underlying disease severity
Aplastic anemia and other serious anemias	Minimize confounding by underlying disease severity
Congenital immune deficiencies	Minimize confounding by underlying disease severity
Down syndrome	Minimize confounding by underlying disease severity
Other lethal chromosomal anomalies	Minimize confounding by underlying disease severity
Fetal metabolic diseases	Minimize confounding by underlying disease severity
Serious neuromuscular diseases	Minimize confounding by underlying disease severity
Hospice case	Minimize confounding by underlying disease severity
Nephrotic syndrome	Minimize confounding by underlying disease severity
Hemochromatosis	Minimize confounding by underlying disease severity
Lupus	Minimize confounding by underlying disease severity
Rheumatoid arthritis	Minimize confounding by underlying disease severity
Crohn's disease	Minimize confounding by underlying disease severity
Ulcerative colitis	Minimize confounding by underlying disease severity
MAX only: Patients with restricted benefits, private insurance, or ineligible managed care plans	Ensure complete capture of MAX claims ¹

eTable 2. Study Definitions for Exposure and Comparator Groups

Group	Generic name or definition
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline
Bupropion	Bupropion
Other antidepressants (used for defining “no antidepressant use”)	<i>Serotonin-norepinephrine reuptake inhibitors (SNRIs):</i> Desvenlafaxine, Duloxetine, Levomilnacipran, Venlafaxine <i>Tricyclic antidepressants (TCAs):</i> Amitriptyline, Amoxapine, Clomipramine, Desipramine, Doxepin, Imipramine, Maprotiline, Nortriptyline, Protriptyline, Trimipramine <i>Monoamine oxidase inhibitors (MAOIs):</i> Isocarboxazid, Phenelzine, Selegiline, Tranylcypromine, Moclobemide <i>Other:</i> Mirtazapine, Nefazodone, Trazodone, Vilazodone, Vortioxetine, Reboxetine, Nomifensine
Psychotherapy	<i>ICD-9 procedure codes:</i> 94.3x, 94.41, 94.42, 94.43, 94.44, 94.51 <i>CPT procedure codes:</i> 90810, 90811, 90812, 90813, 90814, 90815, 90823, 90824, 90826, 90827, 90828, 90829, 90832, 90834, 90833, 90836, 90837, 90838, 90839, 90840, 90845, 90846, 90847, 90849, 90853, 90857, 90804, 90805, 90806, 90807, 90808, 90816, 90818, 90821

No antidepressant use was chosen as the primary comparator group to allow comparability to previous studies and increase precision due to larger sample size. Use of all 3 comparator groups (no antidepressant use, bupropion, psychotherapy) ultimately broadened our understanding of the association between SSRIs and type 2 diabetes in children and adolescents.

eTable 3. Baseline and Time-Varying Covariates Included in Adjustment

Baseline covariates	
Demographics	Substance use
Age at index date (continuous)	Smoking
Gender (Male, Female, Unknown)	Alcohol abuse or dependence
Race (White, Black, American Indian, Asian, Hispanic, Other/Unknown) ^a	Drug abuse or dependence
Region (Northeast, Midwest, South, West, Other)	Cocaine abuse
Calendar year of index date (yearly categories)	Amphetamine use
Medicaid eligibility type (Cash, Disability, Foster care, Low income/Unemployment, Other/unknown) ^a	Opioid abuse
Healthcare utilization	Pain conditions
Number of distinct generic drugs dispensed, excluding antidepressants	Back and neck pain
Number of outpatient visits	Neuropathic pain
Number of mental health (MH) outpatient visits	Musculoskeletal pain
Number of hospitalizations (0, 1, 2+)	Generalized pain
Total length of stay for all hospitalizations (0, 1-5, 6-10, 11+)	Dental pain
Number of mental health hospitalizations (0, 1, 2+)	Pain related to psychological factors
Emergency department visit	Migraine
Nutritionist visit	Other headache
Lab Tests Ordered	Metabolic conditions
Glucose	Obesity
HbA1c	Overweight
Lipid	Underweight
Metabolic screening	Bariatric Surgery
SSRI Indications	Blount's disease
Depression	Acanthosis nigricans
OCD	Hyperlipidemia
PTSD	Hypothyroidism
Social anxiety disorder	Hypothyroid screening
Panic disorder	Other thyroid gland disorder
Generalized anxiety disorder	Nutritional deficiency
Bulimia nervosa	Insulin resistance/metabolic syndrome
Other psychiatric diagnoses	Symptoms related to high blood glucose
ADHD	Other endocrine disorders
Bipolar disorder	Sleep apnea
Schizophrenia	Nonalcoholic fatty liver disease
Psychosis	Weight management
Delirium	Cardiovascular conditions
Personality disorder	Acute MI
Adjustment disorder	Hypertension
Other psychiatric disorders	Cardiac malformations
Tic disorders	Ischemic heart disease
Disruptive behavior disorders	Cardiac arrhythmia
Pervasive development disorders/intellectual disabilities	Cardiac valve disease
Communication & learning disorders	Renal insufficiency
Somatoform spectrum disorders	Congestive heart failure
Eating disorders	CV symptoms
Psychotherapy ^b	Conduction disorder cardiomyopathy

Baseline covariates (continued)	Time-varying covariates
Cardiovascular conditions (continued)	Healthcare utilization
Cerebral vascular disease	Number of distinct generic drugs dispensed, excluding antidepressants
Peripheral vascular disease	Number of outpatient visits
Reproductive conditions	Number of MH outpatient visits
Menstruation disorders	Any hospitalization
Ovarian cysts	Concomitant medication use
Polycystic ovarian syndrome	Antipsychotics
General/other conditions	Anticonvulsants
Sleep disorder	Benzodiazepines
Essential tremor	Mood Stabilizers
Epilepsy or convulsions	Stimulants
Chronic fatigue syndrome	Oral corticosteroids
Maltreatment	Medical diagnoses
Intentional injury/suicide	Depression
Congenital anomalies of digestive system	OCD
Gallbladder disorder	PTSD
Hepatitis B or C	Social anxiety disorder
Rheumatologic disorders	Panic disorder
GI conditions	Generalized anxiety disorder
Chronic liver disease	Bulimia nervosa
Concomitant medication use	ADHD
Antipsychotics	Bipolar disorder
Anticonvulsants	Schizophrenia
Anxiolytics	Psychosis
Barbiturates	Adjustment disorder
Benzodiazepines	Psychotherapy ^b
Mood Stabilizers	Smoking
Other hypnotics	Mood Stabilizers
Stimulants	Stimulants
NSAIDs	Oral corticosteroids
Opioids	
Triptans	
Antihypertensive drugs	
Lipid-lowering drugs	
Other cardiovascular medications ^c	
Oral corticosteroids	
Bronchodilator	
Other asthma medications	
Obesity-related medications	
Thyroid hormone replacement drugs	
Antibiotics	

In intention-to-treat analyses, all baseline covariates were used to conduct propensity score stratification. Within strata of PS, patients in the comparator group were weighted according to the distribution of the SSRI exposed, creating a pseudopopulation where the confounder distribution among the exposed is in concordance with the confounder distribution among the unexposed. $Unexposed\ weight = \frac{N_{exposed\ in\ strata\ i}/N_{total\ exposed}}{N_{unexposed\ in\ strata\ i}/N_{total\ unexposed}}$

In as-treated analyses, all baseline and time-varying covariates were used to estimate inverse probability of treatment weights and inverse probability of censoring weights.

^a MAX only

^b Psychotherapy was not included as a covariate in the SSRI vs. psychotherapy comparison

^c Other cardiovascular medications: anticoagulants, antiplatelets, antiarrhythmic drugs, digoxin

eTable 4. Baseline Characteristics of Children and Adolescents With SSRI Exposure Compared to Those Without Antidepressant Exposure in the Medicaid Analytic eXtract (MAX) ITT Population

	Unadjusted			Accounting for Propensity Score Decile ^a		
	No. (%) of patients		Std diff	No. (%) of patients		Std diff
	SSRIs	Untreated		SSRIs	Untreated	
No. of patients	316,718	632,356	-	316,177	632,235	-
Demographics:						
Age, years; mean (SD)	14.7 (2.1)	14.7 (2.1)	0.00	14.7 (2.1)	14.7 (2.1)	-0.03
Gender, female	197022 (62.3)	345820 (54.7)	0.16	197021 (62.3)	391510 (61.9)	0.01
Race/ethnicity						
White	195863 (61.9)	297791 (47.1)	0.30	195863 (61.9)	397089 (62.8)	-0.02
Black	50194 (15.9)	150119 (23.7)	-0.20	50193 (15.9)	98524 (15.6)	0.01
American Indian	6135 (1.9)	13674 (2.2)	-0.02	6135 (1.9)	12137 (1.9)	0.00
Asian/Pacific Islander	3497 (1.1)	11311 (1.8)	-0.06	3497 (1.1)	6749 (1.1)	0.00
Hispanic/Latino	44363 (14.0)	123650 (19.6)	-0.15	44363 (14.0)	84900 (13.4)	0.02
Other	16126 (5.1)	35811 (5.7)	-0.02	16126 (5.1)	32836 (5.2)	0.00
Year of index date						
2000-2005	118228 (37.4)	236456 (37.4)	0.00	118228 (37.4)	236373 (37.4)	0.00
2006-2010	112624 (35.6)	225248 (35.6)	0.00	112622 (35.6)	227612 (36.0)	-0.01
2011-2015	85326 (27.0)	170652 (27.0)	0.00	85326 (27.0)	168256 (26.6)	0.01
Healthcare utilization:						
No. of distinct generic drugs; median (IQR)	4 (2-7)	3 (1-6)	0.29	4 (1-6)	4 (2-8)	-0.05
No. of outpatient visits; median (IQR)	21 (15-31)	21 (15-31)	-0.06	21 (15-31)	22 (16-33)	-0.04
No. of mental health outpatient visits; median (IQR)	3 (1-11)	3 (0-12)	-0.06	3 (1-11)	3 (1-13)	-0.05
Hospitalization	42485 (13.4)	40675 (6.4)	0.24	42484 (13.4)	80971 (12.8)	0.02
Mental health hospitalization	36324 (11.5)	26812 (4.2)	0.27	36323 (11.5)	67919 (10.7)	0.02
ED visit	152849 (48.3)	277006 (43.8)	0.09	152848 (48.3)	308660 (48.8)	-0.01
Nutritionist visit	2252 (0.7)	5321 (0.8)	-0.01	2252 (0.7)	4430 (0.7)	0.00
SSRI indications:						
Depression	264431 (83.6)	448668 (71.0)	0.31	264430 (83.6)	524946 (83.0)	0.02
OCD	7620 (2.4)	6036 (1.0)	0.11	7619 (2.4)	14334 (2.3)	0.01
PTSD	38923 (12.3)	64637 (10.2)	0.07	38922 (12.3)	77279 (12.2)	0.00
Social anxiety disorder	4327 (1.4)	3188 (0.5)	0.09	4326 (1.4)	7759 (1.2)	0.01
Generalized anxiety disorder	101862 (32.2)	175201 (27.7)	0.10	101861 (32.2)	199338 (31.5)	0.02
Panic disorder	12620 (4.0)	14727 (2.3)	0.10	12619 (4.0)	23063 (3.6)	0.01
Bulimia nervosa	1236 (0.4)	1061 (0.2)	0.04	1236 (0.4)	2017 (0.3)	0.01
Psychiatric conditions:						
Psychotherapy	95354 (30.2)	189194 (29.9)	0.01	95353 (30.2)	195417 (30.9)	-0.02
ADHD	64614 (20.4)	114487 (18.1)	0.06	64614 (20.4)	137315 (21.7)	-0.03
Bipolar disorder	39650 (12.5)	55753 (8.8)	0.12	39649 (12.5)	87479 (13.8)	-0.04
Schizophrenia	3354 (1.1)	5415 (0.9)	0.02	3354 (1.1)	7761 (1.2)	-0.02
Psychosis	12528 (4.0)	13628 (2.2)	0.11	12528 (4.0)	25624 (4.1)	0.00
Adjustment disorder	32281 (10.2)	59790 (9.5)	0.03	32281 (10.2)	65685 (10.4)	-0.01
Intellectual disability	10369 (3.3)	18842 (3.0)	0.02	10368 (3.3)	22987 (3.6)	-0.02
Disruptive behavior disorder	59788 (18.9)	106445 (16.8)	0.05	59787 (18.9)	125485 (19.8)	-0.02
Learning disorders	13134 (4.2)	25249 (4.0)	0.01	13134 (4.2)	27095 (4.3)	-0.01
Eating disorders	2578 (0.8)	2341 (0.4)	0.06	2577 (0.8)	4761 (0.8)	0.01

	Unadjusted			Accounting for Propensity Score Decile ^a		
	No. (%) of patients		Std diff	No. (%) of patients		Std diff
	SSRIs	Untreated		SSRIs	Untreated	
Metabolic conditions:						
Obesity	13896 (4.4)	25932 (4.1)	0.01	13896 (4.4)	28618 (4.5)	-0.01
Overweight	2019 (0.6)	4120 (0.7)	0.00	2019 (0.6)	3953 (0.6)	0.00
Underweight	513 (0.2)	893 (0.1)	0.01	513 (0.2)	1063 (0.2)	0.00
Bariatric surgery	52 (0.0)	163 (0.0)	-0.01	52 (0.0)	105 (0.0)	0.00
Weight management	2245 (0.7)	5308 (0.8)	-0.01	2245 (0.7)	4416 (0.7)	0.00
Hyperlipidemia	3888 (1.2)	8206 (1.3)	-0.01	3888 (1.2)	8270 (1.3)	-0.01
Hypothyroidism	3629 (1.1)	5837 (0.9)	0.02	3629 (1.1)	7951 (1.3)	-0.01
Hypothyroid screening	56315 (17.8)	72664 (11.5)	0.18	56315 (17.8)	117790 (18.6)	-0.02
Insulin resistance/Metabolic syndrome	3548 (1.1)	6643 (1.1)	0.01	3548 (1.1)	7533 (1.2)	-0.01
Nutritional deficiency	1740 (0.6)	2964 (0.5)	0.01	1740 (0.6)	3640 (0.6)	0.00
Other conditions:						
Smoking	5845 (1.8)	8911 (1.4)	0.03	5845 (1.8)	12571 (2.0)	-0.01
Alcohol abuse or dependence	6921 (2.2)	11731 (1.9)	0.02	6921 (2.2)	14451 (2.3)	-0.01
Drug abuse or dependence	19136 (6.1)	32538 (5.1)	0.04	19135 (6.1)	39920 (6.3)	-0.01
Back and neck pain	37156 (11.8)	63013 (10)	0.06	37155 (11.8)	77516 (12.3)	-0.02
Musculoskeletal pain	34592 (10.9)	63674 (10.1)	0.03	34592 (10.9)	70487 (11.1)	-0.01
Hypertension	4313 (1.4)	7645 (1.2)	0.01	4313 (1.4)	10333 (1.6)	-0.02
Cardiovascular symptoms	36722 (11.6)	63638 (10.1)	0.05	36722 (11.6)	75432 (11.9)	-0.01
Menstrual disorders	22190 (7.0)	34836 (5.5)	0.06	22189 (7.0)	46581 (7.4)	-0.01
Polycystic ovarian syndrome	630 (0.2)	997 (0.2)	0.01	630 (0.2)	1374 (0.2)	0.00
Medications:						
Antipsychotics	47628 (15.1)	63108 (10.0)	0.15	47627 (15.1)	103047 (16.3)	-0.03
Stimulants	61785 (19.5)	101833 (16.1)	0.09	61785 (19.5)	130677 (20.7)	-0.03
Benzodiazepines	16774 (5.3)	15583 (2.5)	0.15	16773 (5.3)	34571 (5.5)	-0.01
Barbiturates	3355 (1.1)	4097 (0.6)	0.04	3355 (1.1)	7361 (1.2)	-0.01
Other hypnotics	29683 (9.4)	40870 (6.5)	0.11	29683 (9.4)	62079 (9.8)	-0.01
Anticonvulsants	24405 (7.7)	44386 (7.0)	0.03	24404 (7.7)	57872 (9.2)	-0.05
Mood Stabilizers	22437 (7.1)	42704 (6.8)	0.01	22436 (7.1)	53958 (8.5)	-0.05
NSAIDs	78588 (24.9)	145261 (23.0)	0.04	78586 (24.9)	161330 (25.5)	-0.02
Opioids	73779 (23.3)	123233 (19.5)	0.09	73778 (23.3)	153500 (24.3)	-0.02
Oral corticosteroids	33870 (10.7)	56792 (9.0)	0.06	33870 (10.7)	69550 (11.0)	-0.01
Bronchodilator	59689 (18.9)	105335 (16.7)	0.06	59689 (18.9)	122039 (19.3)	-0.01
Obesity-related drugs	61 (0.0)	132 (0.0)	0.00	61 (0.0)	143 (0.0)	0.00
Antibiotics	190991 (60.4)	340416 (53.8)	0.13	190989 (60.4)	388375 (61.4)	-0.02
Contraceptives	40354 (12.8)	52454 (8.3)	0.15	40353 (12.8)	84277 (13.3)	-0.02
Lab Tests Ordered:						
Glucose	21273 (6.7)	38009 (6.0)	0.03	21272 (6.7)	44896 (7.1)	-0.01
HbA1c	7946 (2.5)	14970 (2.4)	0.01	7946 (2.5)	16842 (2.7)	-0.01
Lipid	28716 (9.1)	57599 (9.1)	0.00	28716 (9.1)	61154 (9.7)	-0.02
Metabolic screening	85993 (27.2)	129891 (20.5)	0.16	85992 (27.2)	178301 (28.2)	-0.02

Abbreviations: ADHD=Attention-deficit/hyperactivity disorder; ED=Emergency department; IQR=Interquartile range; NSAIDs=Nonsteroidal anti-inflammatory drugs; OCD=Obsessive-compulsive disorder; PTSD=Post-traumatic stress disorder; SSRIs=Selective serotonin reuptake inhibitors; std=Standard deviation; std diff=Standardized difference

Numbers reflect before considering first cohort entry.

^a Patients in the nonoverlapping regions of the propensity score distribution were trimmed. Within each propensity score decile, the untreated patients were weighted using the distribution of the SSRI initiators.

eTable 5. Baseline Characteristics of Children and Adolescents With SSRI Exposure Compared to Those Without Antidepressant Exposure in the IBM MarketScan ITT Population

	Unadjusted			Accounting for Propensity Score Decile ^a		
	No. (%) of patients		Std diff	No. (%) of patients		Std diff
	SSRIs	Untreated		SSRIs	Untreated	
No. of patients	211,460	422,920	-	211,459	422,904	-
Demographics:						
Age, years; mean (SD)	15.8 (2.3)	15.8 (2.3)	0.00	15.8 (2.3)	15.9 (2.3)	-0.04
Gender, female	135134 (63.9)	244710 (57.9)	0.12	135133 (63.9)	270295 (63.9)	0.00
Race/ethnicity						
White	N/A	N/A	N/A	N/A	N/A	N/A
Black	N/A	N/A	N/A	N/A	N/A	N/A
American Indian	N/A	N/A	N/A	N/A	N/A	N/A
Asian/Pacific Islander	N/A	N/A	N/A	N/A	N/A	N/A
Hispanic/Latino	N/A	N/A	N/A	N/A	N/A	N/A
Other	N/A	N/A	N/A	N/A	N/A	N/A
Year of index date						
2000-2005	15242 (7.2)	30484 (7.2)	0.00	15242 (7.2)	30348 (7.2)	0.00
2006-2010	76600 (36.2)	153200 (36.2)	0.00	76600 (36.2)	153089 (36.2)	0.00
2011-2015	119618 (56.6)	239236 (56.6)	0.00	119617 (56.6)	239467 (56.6)	0.00
Healthcare utilization:						
No. of distinct generic drugs; median (IQR)	3 (1-5)	2 (1-5)	0.21	3 (1-5)	3 (1-6)	-0.04
No. of outpatient visits; median (IQR)	8 (4-14)	8 (4-14)	0.05	8 (4-14)	8 (4-15)	-0.04
No. of mental health outpatient visits; median (IQR)	2 (0-5)	2 (1-6)	0.02	2 (1-6)	2 (0-6)	-0.04
Hospitalization	18835 (8.9)	19012 (4.5)	0.15	18834 (8.9)	36775 (8.7)	0.01
Mental health hospitalization	16229 (7.7)	12979 (3.1)	0.17	16228 (7.7)	31166 (7.4)	0.01
ED visit	60925 (28.8)	123049 (29.1)	-0.01	60924 (28.8)	123503 (29.2)	-0.01
Nutritionist visit	3008 (1.4)	5799 (1.4)	0.00	3008 (1.4)	6009 (1.4)	0.00
SSRI indications:						
Depression	155341 (73.5)	268072 (63.4)	0.22	155340 (73.5)	308912 (73.0)	0.01
OCD	11908 (5.6)	8714 (2.1)	0.19	11907 (5.6)	22134 (5.2)	0.02
PTSD	6784 (3.2)	10877 (2.6)	0.04	6784 (3.2)	13879 (3.3)	0.00
Social anxiety disorder	6125 (2.9)	4433 (1.0)	0.13	6124 (2.9)	10933 (2.6)	0.02
Generalized anxiety disorder	109745 (51.9)	173578 (41.0)	0.13	109744 (51.9)	217613 (51.5)	0.02
Panic disorder	12662 (6.0)	14103 (3.3)	0.22	12661 (6.0)	23741 (5.6)	0.01
Bulimia nervosa	2208 (1.0)	2187 (0.5)	0.06	2208 (1.0)	4010 (0.9)	0.01
Psychiatric conditions:						
Psychotherapy	89019 (42.1)	206356 (48.8)	-0.13	89019 (42.1)	176522 (41.7)	0.01
ADHD	31850 (15.1)	60079 (14.2)	0.02	31850 (15.1)	68384 (16.2)	-0.03
Bipolar disorder	15650 (7.4)	21420 (5.1)	0.10	15649 (7.4)	35798 (8.5)	-0.04
Schizophrenia	511 (0.2)	965 (0.2)	0.00	511 (0.2)	1289 (0.3)	-0.01
Psychosis	3877 (1.8)	4700 (1.1)	0.06	3877 (1.8)	8015 (1.9)	0.00
Adjustment disorder	11632 (5.5)	18621 (4.4)	0.05	11632 (5.5)	23952 (5.7)	-0.01
Intellectual disability	3724 (1.8)	5799 (1.4)	0.03	3724 (1.8)	8791 (2.1)	-0.02
Disruptive behavior disorder	10020 (4.7)	16547 (3.9)	0.04	10020 (4.7)	22106 (5.2)	-0.02
Learning disorders	2228 (1.1)	4444 (1.1)	0.00	2228 (1.1)	4986 (1.2)	-0.01
Eating disorders	4897 (2.3)	4210 (1.0)	0.10	4896 (2.3)	9355 (2.2)	0.01
Metabolic conditions:						

	Unadjusted			Accounting for Propensity Score Decile ^a		
	No. (%) of patients		Std diff	No. (%) of patients		Std diff
	SSRIs	Untreated		SSRIs	Untreated	
Obesity	4017 (1.9)	8634 (2.0)	-0.01	4017 (1.9)	8309 (2.0)	0.00
Overweight	1290 (0.6)	2857 (0.7)	-0.01	1290 (0.6)	2624 (0.6)	0.00
Underweight	641 (0.3)	861 (0.2)	0.02	641 (0.3)	1240 (0.3)	0.00
Bariatric surgery	9 (0.0)	99 (0.0)	-0.02	9 (0.0)	35 (0.0)	-0.01
Weight management	3000 (1.4)	5787 (1.4)	0.00	3000 (1.4)	5988 (1.4)	0.00
Hyperlipidemia	2479 (1.2)	5745 (1.4)	-0.02	2479 (1.2)	5128 (1.2)	0.00
Hypothyroidism	2963 (1.4)	5301 (1.3)	0.01	2962 (1.4)	6473 (1.5)	-0.01
Hypothyroid screening	40537 (19.2)	53568 (12.7)	0.18	40536 (19.2)	83348 (19.7)	-0.01
Insulin resistance/Metabolic syndrome	2026 (1.0)	4226 (1.0)	0.00	2026 (1.0)	4299 (1.0)	-0.01
Nutritional deficiency	2581 (1.2)	4145 (1.0)	0.02	2581 (1.2)	5213 (1.2)	0.00
Other conditions:						
Smoking	3017 (1.4)	7229 (1.7)	-0.02	3017 (1.4)	7048 (1.7)	-0.02
Alcohol abuse or dependence	3225 (1.5)	6700 (1.6)	0.00	3225 (1.5)	7024 (1.7)	-0.01
Drug abuse or dependence	7603 (3.6)	13986 (3.3)	0.02	7603 (3.6)	16589 (3.9)	-0.02
Back and neck pain	27864 (13.2)	60261 (14.2)	-0.03	27864 (13.2)	57660 (13.6)	-0.01
Musculoskeletal pain	19980 (9.4)	46988 (11.1)	-0.05	19980 (9.4)	39881 (9.4)	0.00
Hypertension	1622 (0.8)	3562 (0.8)	-0.01	1622 (0.8)	3464 (0.8)	-0.01
Cardiovascular symptoms	21041 (10.0)	41456 (9.8)	0.00	21041 (10)	43325 (10.2)	-0.01
Menstrual disorders	14922 (7.1)	25951 (6.1)	0.04	14922 (7.1)	30715 (7.3)	-0.01
Polycystic ovarian syndrome	759 (0.4)	1466 (0.3)	0.00	759 (0.4)	1601 (0.4)	0.00
Medications:						
Antipsychotics	10524 (5.0)	13927 (3.3)	0.08	10524 (5.0)	23851 (5.6)	-0.03
Stimulants	33066 (15.6)	59385 (14.0)	0.04	33066 (15.6)	70757 (16.7)	-0.03
Benzodiazepines	20097 (9.5)	15938 (3.8)	0.23	20096 (9.5)	40306 (9.5)	0.00
Barbiturates	1471 (0.7)	1957 (0.5)	0.03	1471 (0.7)	3154 (0.7)	-0.01
Other hypnotics	9412 (4.5)	9556 (2.3)	0.12	9412 (4.5)	19433 (4.6)	-0.01
Anticonvulsants	8286 (3.9)	16142 (3.8)	0.01	8286 (3.9)	20214 (4.8)	-0.04
Mood Stabilizers	7052 (3.3)	14464 (3.4)	0.00	7052 (3.3)	17627 (4.2)	-0.04
NSAIDs	23798 (11.3)	43412 (10.3)	0.03	23798 (11.3)	49643 (11.7)	-0.02
Opioids	44800 (21.2)	82110 (19.4)	0.04	44800 (21.2)	92459 (21.9)	-0.02
Oral corticosteroids	22717 (10.7)	41794 (9.9)	0.03	22717 (10.7)	46381 (11.0)	-0.01
Bronchodilator	27553 (13.0)	51385 (12.2)	0.03	27553 (13)	55314 (13.1)	0.00
Obesity-related drugs	65 (0.0)	146 (0.0)	0.00	65 (0.0)	141 (0.0)	0.00
Antibiotics	125287 (59.2)	232052 (54.9)	0.09	125286 (59.2)	251490 (59.5)	0.00
Contraceptives	41265 (19.5)	59755 (14.1)	0.14	41265 (19.5)	85294 (20.2)	-0.02
Lab Tests Ordered:						
Glucose	12750 (6.0)	23497 (5.6)	0.02	12750 (6.0)	26840 (6.3)	-0.01
HbA1c	4969 (2.3)	9796 (2.3)	0.00	4969 (2.3)	10604 (2.5)	-0.01
Lipid	23309 (11.0)	45535 (10.8)	0.01	23309 (11.0)	47842 (11.3)	-0.01
Metabolic screening	59735 (28.2)	93895 (22.2)	0.14	59734 (28.2)	122888 (29.1)	-0.02

Abbreviations: ADHD=Attention-deficit/hyperactivity disorder; ED=Emergency department; IQR=Interquartile range; NSAIDs=Nonsteroidal anti-inflammatory drugs; OCD=Obsessive-compulsive disorder; PTSD=Post-traumatic stress disorder; SSRIs=Selective serotonin reuptake inhibitors; std=Standard deviation; std diff=Standardized difference

Numbers reflect before considering first cohort entry. Race/ethnicity is not available in the MarketScan database.

^a Patients in the nonoverlapping regions of the propensity score distribution were trimmed. Within each propensity score decile, the untreated patients were weighted using the distribution of the SSRI initiators.

eTable 6. Baseline Characteristics of Children and Adolescents With SSRI Compared With Bupropion Exposure in the Medicaid Analytic eXtract (MAX) ITT Population

	Unadjusted			Accounting for Propensity Score Decile ^a		
	No. (%) of patients		Std diff	No. (%) of patients		Std diff
	SSRIs	Bupropion		SSRIs	Bupropion	
No. of patients	316,718	35,476	-	316,009	35,475	-
Demographics:						
Age, years; mean (SD)	14.7 (2.1)	14.5 (2.1)	0.08	14.7 (2.1)	14.7 (2.2)	-0.02
Gender, female	197022 (62.3)	16212 (45.7)	0.34	196874 (62.3)	22350 (63)	-0.01
Race/ethnicity						
White	195863 (61.9)	20573 (58.0)	0.08	195758 (61.9)	22209 (62.6)	-0.01
Black	50194 (15.9)	7472 (21.1)	-0.13	50174 (15.9)	5772 (16.3)	-0.01
American Indian	6135 (1.9)	700 (2.0)	0.00	6130 (1.9)	682 (1.9)	0.00
Asian/Pacific Islander	3497 (1.1)	322 (0.9)	0.02	3492 (1.1)	348 (1.0)	0.01
Hispanic/Latino	44363 (14)	4388 (12.4)	0.05	44336 (14.0)	4736 (13.4)	0.02
Other	16126 (5.1)	2021 (5.7)	-0.03	16119 (5.1)	1728 (4.9)	0.01
Year of index date						
2000-2005	118228 (37.4)	16664 (47.0)	-0.19	118216 (37.4)	12895 (36.3)	0.02
2006-2010	112624 (35.6)	12334 (34.8)	0.02	112579 (35.6)	12735 (35.9)	-0.01
2011-2015	85326 (27.0)	6478 (18.3)	0.21	85214 (27.0)	9845 (27.8)	-0.02
Healthcare utilization:						
No. of distinct generic drugs; median (IQR)	4 (2-7)	4 (2-7)	0.05	4 (2-7)	2 (2-8)	-0.06
No. of outpatient visits; median (IQR)	21 (15-31)	22 (16-35)	-0.21	21 (15-31)	22 (16-33)	-0.06
No. of mental health outpatient visits; median (IQR)	3 (1-11)	6 (1-18)	-0.15	3 (1-11)	4 (1-13)	-0.05
Hospitalization	42489 (13.4)	4949 (14.0)	-0.01	42422 (13.4)	5218 (14.7)	-0.04
Mental health hospitalization	36324 (11.5)	4499 (12.7)	-0.04	36267 (11.5)	4508 (12.7)	-0.04
ED visit	152849 (48.3)	16014 (45.1)	0.06	152727 (48.3)	17639 (49.7)	-0.03
Nutritionist visit	2252 (0.7)	213 (0.6)	0.01	2245 (0.7)	259 (0.7)	0.00
SSRI indications:						
Depression	264431 (83.6)	31521 (88.9)	-0.15	264314 (83.6)	30120 (84.9)	-0.03
OCD	7620 (2.4)	279 (0.8)	0.13	7527 (2.4)	801 (2.3)	0.01
PTSD	38923 (12.3)	4386 (12.4)	0.00	38891 (12.3)	4548 (12.8)	-0.02
Social anxiety disorder	4327 (1.4)	122 (0.3)	0.11	4260 (1.3)	463 (1.3)	0.00
Generalized anxiety disorder	101862 (32.2)	5990 (16.9)	0.19	101700 (32.2)	11631 (32.8)	0.02
Panic disorder	12620 (4.0)	347 (1.0)	0.36	12496 (4.0)	1266 (3.6)	-0.01
Bulimia nervosa	1236 (0.4)	38 (0.1)	0.06	1217 (0.4)	139 (0.4)	0.00
Psychiatric conditions:						
Psychotherapy	95354 (30.2)	12867 (36.3)	-0.13	95296 (30.2)	11323 (31.9)	-0.04
ADHD	64614 (20.4)	13678 (38.6)	-0.41	64607 (20.4)	7838 (22.1)	-0.04
Bipolar disorder	39650 (12.5)	7196 (20.3)	-0.21	39642 (12.5)	5105 (14.4)	-0.05
Schizophrenia	3354 (1.1)	555 (1.6)	-0.04	3351 (1.1)	456 (1.3)	-0.02
Psychosis	12528 (4.0)	1503 (4.2)	-0.01	12506 (4.0)	1544 (4.4)	-0.02
Adjustment disorder	32281 (10.2)	4131 (11.6)	-0.05	32264 (10.2)	3795 (10.7)	-0.02
Intellectual disability	10369 (3.3)	1059 (3.0)	0.02	10356 (3.3)	1219 (3.4)	-0.01
Disruptive behavior disorder	59788 (18.9)	10655 (30.0)	-0.26	59774 (18.9)	7301 (20.6)	-0.04
Learning disorders	13134 (4.2)	1764 (5.0)	-0.04	13122 (4.2)	1504 (4.2)	0.00
Eating disorders	2578 (0.8)	134 (0.4)	0.06	2559 (0.8)	290 (0.8)	0.00
Metabolic conditions:						

	Unadjusted			Accounting for Propensity Score Decile ^a		
	No. (%) of patients		Std diff	No. (%) of patients		Std diff
	SSRIs	Bupropion		SSRIs	Bupropion	
Obesity	13896 (4.4)	2130 (6.0)	-0.07	13892 (4.4)	1661 (4.7)	-0.01
Overweight	2019 (0.6)	205 (0.6)	0.01	2018 (0.6)	237 (0.7)	0.00
Underweight	513 (0.2)	23 (0.1)	0.03	503 (0.2)	44 (0.1)	0.01
Bariatric surgery	52 (0.0)	<11 (0.0)	0.00	52 (0.0)	<11 (0.0)	-0.01
Weight management	2245 (0.7)	212 (0.6)	0.01	2238 (0.7)	256 (0.7)	0.00
Hyperlipidemia	3888 (1.2)	535 (1.5)	-0.02	3883 (1.2)	467 (1.3)	-0.01
Hypothyroidism	3629 (1.1)	460 (1.3)	-0.01	3628 (1.1)	452 (1.3)	-0.01
Hypothyroid screening	56315 (17.8)	6454 (18.2)	-0.01	56250 (17.8)	6482 (18.3)	-0.01
Insulin resistance/Metabolic syndrome	3548 (1.1)	448 (1.3)	-0.01	3547 (1.1)	451 (1.3)	-0.01
Nutritional deficiency	1740 (0.6)	118 (0.3)	0.03	1727 (0.5)	195 (0.5)	0.00
Other conditions:						
Smoking	5845 (1.8)	938 (2.6)	-0.05	5845 (1.8)	793 (2.2)	-0.03
Alcohol abuse or dependence	6921 (2.2)	1132 (3.2)	-0.06	6920 (2.2)	871 (2.5)	-0.02
Drug abuse or dependence	19136 (6.1)	3305 (9.3)	-0.12	19130 (6.1)	2340 (6.6)	-0.02
Back and neck pain	37156 (11.8)	3382 (9.5)	0.07	37131 (11.7)	4362 (12.3)	-0.02
Musculoskeletal pain	34592 (10.9)	3817 (10.8)	0.01	34573 (10.9)	4080 (11.5)	-0.02
Hypertension	4313 (1.4)	530 (1.5)	-0.01	4309 (1.4)	530 (1.5)	-0.01
Cardiovascular symptoms	36722 (11.6)	3041 (8.6)	0.10	36655 (11.6)	4111 (11.6)	0.00
Menstrual disorders	22190 (7.0)	1780 (5.0)	0.08	22175 (7.0)	2712 (7.6)	-0.02
Polycystic ovarian syndrome	630 (0.2)	69 (0.2)	0.00	630 (0.2)	80 (0.2)	-0.01
Medications:						
Antipsychotics	47628 (15.1)	9087 (25.6)	-0.26	47612 (15.1)	6269 (17.7)	-0.07
Stimulants	61785 (19.5)	11906 (33.6)	-0.32	61778 (19.5)	7807 (22)	-0.06
Benzodiazepines	16774 (5.3)	996 (2.8)	0.00	16704 (5.3)	1891 (5.3)	-0.02
Barbiturates	3355 (1.1)	223 (0.6)	0.13	3346 (1.1)	437 (1.2)	0.00
Other hypnotics	29683 (9.4)	3284 (9.3)	0.00	29656 (9.4)	3447 (9.7)	-0.01
Anticonvulsants	24405 (7.7)	4949 (14.0)	-0.20	24383 (7.7)	3266 (9.2)	-0.05
Mood Stabilizers	22437 (7.1)	5000 (14.1)	-0.23	22428 (7.1)	3011 (8.5)	-0.05
NSAIDs	78588 (24.9)	7388 (20.8)	0.10	78532 (24.9)	8984 (25.3)	-0.01
Opioids	73779 (23.3)	6956 (19.6)	0.09	73738 (23.3)	8600 (24.2)	-0.02
Oral corticosteroids	33870 (10.7)	3161 (8.9)	0.06	33840 (10.7)	3863 (10.9)	-0.01
Bronchodilator	59689 (18.9)	6428 (18.1)	0.02	59656 (18.9)	6856 (19.3)	-0.01
Obesity-related drugs	61 (0.0)	<11 (0.0)	0.00	61 (0.0)	<11 (0.0)	0.00
Antibiotics	190991 (60.4)	19136 (53.9)	0.13	190874 (60.4)	21737 (61.3)	-0.02
Contraceptives	40354 (12.8)	2989 (8.4)	0.14	40325 (12.8)	4776 (13.5)	-0.02
Lab Tests Ordered:						
Glucose	21273 (6.7)	2529 (7.1)	-0.02	21248 (6.7)	2489 (7.0)	-0.01
HbA1c	7946 (2.5)	1024 (2.9)	-0.02	7943 (2.5)	974 (2.7)	-0.01
Lipid	28716 (9.1)	4135 (11.7)	-0.08	28702 (9.1)	3323 (9.4)	-0.01
Metabolic screening	85993 (27.2)	9125 (25.7)	0.03	85892 (27.2)	10015 (28.2)	-0.02

Abbreviations: ADHD=Attention-deficit/hyperactivity disorder; ED=Emergency department; IQR=Interquartile range; NSAIDs=Nonsteroidal anti-inflammatory drugs; OCD=Obsessive-compulsive disorder; PTSD=Post-traumatic stress disorder; SSRIs=Selective serotonin reuptake inhibitors; std=Standard deviation; std diff=Standardized difference

Numbers reflect before considering first cohort entry. Counts less than 11 denoted as <11 to protect patient privacy.

^a Patients in the nonoverlapping regions of the propensity score distribution were trimmed. Within each propensity score decile, the bupropion patients were weighted using the distribution of the SSRI initiators.

eTable 7. Baseline Characteristics of Children and Adolescents With SSRI Compared With Bupropion Exposure in the IBM MarketScan ITT Population

	Unadjusted			Accounting for Propensity Score Decile ^a		
	No. (%) of patients		Std diff	No. (%) of patients		Std diff
	SSRIs	Bupropion		SSRIs	Bupropion	
No. of patients	211,460	14,371	-	210,734	14,367	-
Demographics:						
Age, years; mean (SD)	15.8 (2.3)	16.2 (2.2)	-0.15	15.8 (2.3)	15.9 (2.3)	-0.05
Gender, female	135134 (63.9)	6990 (48.6)	0.31	134525 (63.8)	9303 (64.8)	-0.02
Race/ethnicity						
White	N/A	N/A	N/A	N/A	N/A	N/A
Black	N/A	N/A	N/A	N/A	N/A	N/A
American Indian	N/A	N/A	N/A	N/A	N/A	N/A
Asian/Pacific Islander	N/A	N/A	N/A	N/A	N/A	N/A
Hispanic/Latino	N/A	N/A	N/A	N/A	N/A	N/A
Other	N/A	N/A	N/A	N/A	N/A	N/A
Year of index date						
2000-2005	15242 (7.2)	1704 (11.9)	-0.16	15236 (7.2)	1016 (7.1)	0.01
2006-2010	76600 (36.2)	5933 (41.3)	-0.10	76455 (36.3)	5078 (35.3)	0.02
2011-2015	119618 (56.6)	6734 (46.9)	0.20	119043 (56.5)	8273 (57.6)	-0.02
Healthcare utilization:						
No. of distinct generic drugs; median (IQR)	3 (1-5)	3 (2-6)	-0.08	3 (1-5)	3 (2-6)	-0.06
No. of outpatient visits; median (IQR)	8 (4-14)	8 (15-16)	-0.17	8 (4-14)	8 (4-15)	-0.04
No. of mental health outpatient visits; median (IQR)	2 (0-5)	3 (1-8)	-0.08	2 (1-6)	2 (1-6)	-0.05
Hospitalization	18835 (8.9)	1739 (12.1)	-0.11	18712 (8.9)	1482 (10.3)	-0.05
Mental health hospitalization	16229 (7.7)	1598 (11.1)	-0.13	16119 (7.6)	1323 (9.2)	-0.06
ED visit	60925 (28.8)	4359 (30.3)	-0.03	60642 (28.8)	4400 (30.6)	-0.04
Nutritionist visit	3008 (1.4)	174 (1.2)	0.02	2943 (1.4)	160 (1.1)	0.03
SSRI indications:						
Depression	155341 (73.5)	12734 (88.6)	-0.39	155010 (73.6)	10692 (74.4)	-0.02
OCD	11908 (5.6)	176 (1.2)	0.24	11284 (5.4)	667 (4.6)	0.03
PTSD	6784 (3.2)	384 (2.7)	0.03	6738 (3.2)	514 (3.6)	-0.02
Social anxiety disorder	6125 (2.9)	136 (0.9)	0.14	5919 (2.8)	409 (2.8)	0.00
Generalized anxiety disorder	109745 (51.9)	3989 (27.8)	0.22	109052 (51.7)	7538 (52.5)	-0.03
Panic disorder	12662 (6.0)	258 (1.8)	0.51	12310 (5.8)	957 (6.7)	-0.01
Bulimia nervosa	2208 (1.0)	45 (0.3)	0.09	2138 (1.0)	173 (1.2)	-0.02
Psychiatric conditions:						
Psychotherapy	89019 (42.1)	7323 (51)	-0.18	88654 (42.1)	5997 (41.7)	0.01
ADHD	31850 (15.1)	4550 (31.7)	-0.40	31841 (15.1)	2453 (17.1)	-0.05
Bipolar disorder	15650 (7.4)	2164 (15.1)	-0.24	15621 (7.4)	1331 (9.3)	-0.07
Schizophrenia	511 (0.2)	77 (0.5)	-0.05	511 (0.2)	50 (0.3)	-0.02
Psychosis	3877 (1.8)	343 (2.4)	-0.04	3850 (1.8)	322 (2.2)	-0.03
Adjustment disorder	11632 (5.5)	865 (6)	-0.02	11592 (5.5)	779 (5.4)	0.00
Intellectual disability	3724 (1.8)	190 (1.3)	0.04	3677 (1.7)	300 (2.1)	-0.03
Disruptive behavior disorder	10020 (4.7)	1134 (7.9)	-0.13	10003 (4.7)	757 (5.3)	-0.02
Learning disorders	2228 (1.1)	195 (1.4)	-0.03	2219 (1.1)	167 (1.2)	-0.01
Eating disorders	4897 (2.3)	112 (0.8)	0.12	4713 (2.2)	342 (2.4)	-0.01
Metabolic conditions:						

	Unadjusted			Accounting for Propensity Score Decile ^a		
	No. (%) of patients		Std diff	No. (%) of patients		Std diff
	SSRIs	Bupropion		SSRIs	Bupropion	
Obesity	4017 (1.9)	478 (3.3)	-0.09	4012 (1.9)	335 (2.3)	-0.03
Overweight	1290 (0.6)	113 (0.8)	-0.02	1282 (0.6)	92 (0.6)	0.00
Underweight	641 (0.3)	15 (0.1)	0.04	587 (0.3)	38 (0.3)	0.00
Bariatric surgery	<11 (0.0)	<11 (0.0)	0.00	<11 (0.0)	<11 (0.0)	0.00
Weight management	3000 (1.4)	174 (1.2)	0.02	2943 (1.4)	160 (1.1)	0.03
Hyperlipidemia	2479 (1.2)	237 (1.6)	-0.04	2473 (1.2)	168 (1.2)	0.00
Hypothyroidism	2963 (1.4)	236 (1.6)	-0.02	2950 (1.4)	214 (1.5)	-0.01
Hypothyroid screening	40537 (19.2)	2750 (19.1)	0.00	40327 (19.1)	2968 (20.7)	-0.04
Insulin resistance/Metabolic syndrome	2026 (1.0)	198 (1.4)	-0.04	2020 (1.0)	181 (1.3)	-0.03
Nutritional deficiency	2581 (1.2)	162 (1.1)	0.01	2537 (1.2)	159 (1.1)	0.01
Other conditions:						
Smoking	3017 (1.4)	410 (2.9)	-0.10	3017 (1.4)	295 (2.1)	-0.05
Alcohol abuse or dependence	3225 (1.5)	474 (3.3)	-0.12	3222 (1.5)	271 (1.9)	-0.03
Drug abuse or dependence	7603 (3.6)	1134 (7.9)	-0.19	7599 (3.6)	642 (4.5)	-0.04
Back and neck pain	27864 (13.2)	1805 (12.6)	0.02	27775 (13.2)	2000 (13.9)	-0.02
Musculoskeletal pain	19980 (9.4)	1317 (9.2)	0.01	19897 (9.4)	1367 (9.5)	0.00
Hypertension	1622 (0.8)	157 (1.1)	-0.03	1616 (0.8)	131 (0.9)	-0.02
Cardiovascular symptoms	21041 (10.0)	1153 (8.0)	0.07	20904 (9.9)	1499 (10.4)	-0.02
Menstrual disorders	14922 (7.1)	740 (5.1)	0.08	14832 (7.0)	1099 (7.7)	-0.02
Polycystic ovarian syndrome	759 (0.4)	61 (0.4)	-0.01	757 (0.4)	68 (0.5)	-0.02
Medications:						
Antipsychotics	10524 (5.0)	1537 (10.7)	-0.21	10501 (5.0)	988 (6.9)	-0.08
Stimulants	33066 (15.6)	4133 (28.8)	-0.32	33029 (15.7)	2852 (19.8)	-0.11
Benzodiazepines	20097 (9.5)	806 (5.6)	-0.01	19881 (9.4)	1503 (10.5)	-0.03
Barbiturates	1471 (0.7)	77 (0.5)	0.15	1466 (0.7)	104 (0.7)	-0.03
Other hypnotics	9412 (4.5)	677 (4.7)	-0.01	9373 (4.4)	692 (4.8)	-0.02
Anticonvulsants	8286 (3.9)	1234 (8.6)	-0.19	8265 (3.9)	777 (5.4)	-0.07
Mood Stabilizers	7052 (3.3)	1212 (8.4)	-0.22	7042 (3.3)	659 (4.6)	-0.06
NSAIDs	23798 (11.3)	1541 (10.7)	0.02	23734 (11.3)	1752 (12.2)	-0.03
Opioids	44800 (21.2)	3226 (22.4)	-0.03	44695 (21.2)	3235 (22.5)	-0.03
Oral corticosteroids	22717 (10.7)	1389 (9.7)	0.04	22638 (10.7)	1595 (11.1)	-0.01
Bronchodilator	27553 (13)	1739 (12.1)	0.03	27445 (13)	1925 (13.4)	-0.01
Obesity-related drugs	65 (0.0)	17 (0.1)	-0.03	65 (0.0)	<11 (0.0)	0.00
Antibiotics	125287 (59.2)	8234 (57.3)	0.04	124844 (59.2)	8663 (60.3)	-0.02
Contraceptives	41265 (19.5)	2162 (15)	0.12	41161 (19.5)	3080 (21.4)	-0.05
Lab Tests Ordered:						
Glucose	12750 (6.0)	1017 (7.1)	-0.04	12697 (6.0)	890 (6.2)	-0.01
HbA1c	4969 (2.3)	473 (3.3)	-0.06	4951 (2.3)	363 (2.5)	-0.01
Lipid	23309 (11.0)	1891 (13.2)	-0.07	23222 (11.0)	1683 (11.7)	-0.02
Metabolic screening	59735 (28.2)	3903 (27.2)	0.02	59410 (28.2)	4330 (30.1)	-0.04

Abbreviations: ADHD=Attention-deficit/hyperactivity disorder; ED=Emergency department; IQR=Interquartile range; NSAIDs=Nonsteroidal anti-inflammatory drugs; OCD=Obsessive-compulsive disorder; PTSD=Post-traumatic stress disorder; SSRIs=Selective serotonin reuptake inhibitors; std=Standard deviation; std diff=Standardized difference

Numbers reflect before considering first cohort entry. Counts less than 11 denoted as <11 to protect patient privacy. Race/ethnicity is not available in the MarketScan database.

^a Patients in the nonoverlapping regions of the propensity score distribution were trimmed. Within each propensity score decile, the bupropion patients were weighted using the distribution of the SSRI initiators.

eTable 8. Baseline Characteristics of Children and Adolescents With SSRI Compared With Psychotherapy Exposure in the Medicaid Analytic eXtract (MAX) ITT Population

	Unadjusted			Accounting for Propensity Score Decile ^a		
	No. (%) of patients		Std diff	No. (%) of patients		Std diff
	SSRIs	Psychotherapy		SSRIs	Psychotherapy	
No. of patients	316,718	227,247	-	316,161	227,143	-
Demographics:						
Age, years; mean (SD)	14.7 (2.1)	13.9 (2.1)	0.37	14.7 (2.1)	14.6 (2.1)	0.01
Gender, female	197022 (62.3)	130382 (57.4)	0.10	197010 (62.3)	137248 (60.4)	0.04
Race/ethnicity						
White	195863 (61.9)	115475 (50.8)	0.23	195852 (61.9)	140428 (61.8)	0.00
Black	50194 (15.9)	57423 (25.3)	-0.23	50193 (15.9)	38481 (16.9)	-0.03
American Indian	6135 (1.9)	5428 (2.4)	-0.03	6135 (1.9)	4639 (2.0)	-0.01
Asian/Pacific Islander	3497 (1.1)	3488 (1.5)	-0.04	3497 (1.1)	2473 (1.1)	0.00
Hispanic/Latino	44363 (14)	33822 (14.9)	-0.02	44359 (14.0)	28705 (12.6)	0.04
Other	16126 (5.1)	11611 (5.1)	0.00	16125 (5.1)	12408 (5.5)	-0.02
Year of index date						
2000-2005	118228 (37.4)	67831 (29.8)	0.16	118217 (37.4)	85061 (37.4)	0.00
2006-2010	112624 (35.6)	91733 (40.4)	-0.10	112620 (35.6)	82110 (36.2)	-0.01
2011-2015	85326 (27.0)	67683 (29.8)	-0.06	85324 (27.0)	59964 (26.4)	0.01
Healthcare utilization:						
No. of distinct generic drugs; median (IQR)	4 (2-7)	2 (0-5)	0.51	4 (2-7)	4 (2-8)	-0.02
No. of outpatient visits; median (IQR)	21 (15-31)	18 (14-24)	0.22	21 (15-31)	21 (16-30)	-0.07
No. of mental health outpatient visits; median (IQR)	3 (1-11)	2 (2-4)	0.24	3 (1-11)	3 (2-7)	-0.07
Hospitalization	42485 (13.4)	10792 (4.7)	0.31	42473 (13.4)	27629 (12.2)	0.04
Mental health hospitalization	36324 (11.5)	7164 (3.2)	0.32	36313 (11.5)	23135 (10.2)	0.04
ED visit	152849 (48.3)	83611 (36.8)	0.24	152833 (48.3)	110023 (48.4)	0.00
Nutritionist visit	2252 (0.7)	1820 (0.8)	-0.01	2251 (0.7)	1598 (0.7)	0.00
SSRI indications:						
Depression	264431 (83.6)	173043 (76.1)	0.19	264415 (83.6)	186999 (82.3)	0.03
OCD	7620 (2.4)	1789 (0.8)	0.13	7614 (2.4)	5218 (2.3)	0.01
PTSD	38923 (12.3)	24982 (11.0)	0.04	38918 (12.3)	27399 (12.1)	0.01
Social anxiety disorder	4327 (1.4)	1540 (0.7)	0.07	4323 (1.4)	2940 (1.3)	0.01
Generalized anxiety disorder	101862 (32.2)	56115 (24.7)	0.17	101848 (32.2)	70815 (31.2)	0.03
Panic disorder	12620 (4.0)	2811 (1.2)	0.17	12616 (4.0)	7705 (3.4)	0.02
Bulimia nervosa	1236 (0.4)	345 (0.2)	0.05	1236 (0.4)	734 (0.3)	0.01
Psychiatric conditions:						
ADHD	64614 (20.4)	33362 (14.7)	0.15	64610 (20.4)	52847 (23.3)	-0.07
Bipolar disorder	39650 (12.5)	13455 (5.9)	0.23	39641 (12.5)	32080 (14.1)	-0.05
Schizophrenia	3354 (1.1)	1016 (0.4)	0.07	3352 (1.1)	2727 (1.2)	-0.01
Psychosis	12528 (4.0)	3471 (1.5)	0.15	12526 (4.0)	8879 (3.9)	0.00
Adjustment disorder	32281 (10.2)	25410 (11.2)	-0.03	32277 (10.2)	24243 (10.7)	-0.02
Intellectual disability	10369 (3.3)	4102 (1.8)	0.09	10362 (3.3)	8739 (3.8)	-0.03
Disruptive behavior disorder	59788 (18.9)	34532 (15.2)	0.10	59780 (18.9)	47085 (20.7)	-0.05
Learning disorders	13134 (4.2)	7711 (3.4)	0.04	13131 (4.2)	10501 (4.6)	-0.02
Eating disorders	2578 (0.8)	967 (0.4)	0.05	2577 (0.8)	1743 (0.8)	0.01
Metabolic conditions:						

	Unadjusted			Accounting for Propensity Score Decile ^a		
	No. (%) of patients		Std diff	No. (%) of patients		Std diff
	SSRIs	Psychotherapy		SSRIs	Psychotherapy	
Obesity	13896 (4.4)	8275 (3.6)	0.04	13892 (4.4)	9972 (4.4)	0.00
Overweight	2019 (0.6)	1626 (0.7)	-0.01	2019 (0.6)	1361 (0.6)	0.01
Underweight	513 (0.2)	279 (0.1)	0.01	513 (0.2)	363 (0.2)	0.00
Bariatric surgery	52 (0.0)	77 (0.0)	-0.01	52 (0.0)	53 (0.0)	0.00
Weight management	2245 (0.7)	1815 (0.8)	-0.01	2244 (0.7)	1591 (0.7)	0.00
Hyperlipidemia	3888 (1.2)	2131 (0.9)	0.03	3888 (1.2)	2822 (1.2)	0.00
Hypothyroidism	3629 (1.1)	1296 (0.6)	0.06	3629 (1.1)	2610 (1.1)	0.00
Hypothyroid screening	56315 (17.8)	18580 (8.2)	0.29	56305 (17.8)	40039 (17.6)	0.00
Insulin resistance/Metabolic syndrome	1740 (0.6)	950 (0.4)	0.01	3547 (1.1)	2707 (1.2)	-0.01
Nutritional deficiency	1740 (0.6)	950 (0.4)	0.02	1740 (0.6)	1324 (0.6)	0.00
Other conditions:						
Smoking	5845 (1.8)	1600 (0.7)	0.10	5843 (1.8)	4025 (1.8)	0.01
Alcohol abuse or dependence	6921 (2.2)	2755 (1.2)	0.08	6921 (2.2)	5009 (2.2)	0.00
Drug abuse or dependence	19136 (6.1)	7496 (3.3)	0.13	19136 (6.1)	13969 (6.2)	0.00
Back and neck pain	37156 (11.8)	17165 (7.6)	0.14	37148 (11.7)	26770 (11.8)	0.00
Musculoskeletal pain	34592 (10.9)	20396 (9.0)	0.07	34588 (10.9)	25285 (11.1)	-0.01
Hypertension	4313 (1.4)	1764 (0.8)	0.06	4312 (1.4)	3212 (1.4)	0.00
Cardiovascular symptoms	36722 (11.6)	16121 (7.1)	0.16	36716 (11.6)	26358 (11.6)	0.00
Menstrual disorders	22190 (7.0)	8345 (3.7)	0.15	22187 (7.0)	16033 (7.1)	0.00
Polycystic ovarian syndrome	630 (0.2)	290 (0.1)	0.02	630 (0.2)	468 (0.2)	0.00
Medications:						
Antipsychotics	47628 (15.1)	10249 (4.5)	0.36	47614 (15.1)	36312 (16.0)	-0.03
Stimulants	61785 (19.5)	25735 (11.3)	0.23	61778 (19.5)	51593 (22.7)	-0.08
Benzodiazepines	16774 (5.3)	3038 (1.3)	0.22	16759 (5.3)	10625 (4.7)	0.03
Barbiturates	3355 (1.1)	964 (0.4)	0.07	3352 (1.1)	2299 (1.0)	0.00
Other hypnotics	29683 (9.4)	10249 (4.5)	0.19	29675 (9.4)	21139 (9.3)	0.00
Anticonvulsants	24405 (7.7)	7952 (3.5)	0.18	24392 (7.7)	21354 (9.4)	-0.06
Mood Stabilizers	22437 (7.1)	7495 (3.3)	0.17	22427 (7.1)	20472 (9.0)	-0.07
NSAIDs	78588 (24.9)	38619 (17)	0.19	78573 (24.9)	55767 (24.6)	0.01
Opioids	73779 (23.3)	35233 (15.5)	0.20	73770 (23.3)	53262 (23.4)	0.00
Oral corticosteroids	33870 (10.7)	18946 (8.3)	0.08	33865 (10.7)	25001 (11)	-0.01
Bronchodilator	59689 (18.9)	35323 (15.5)	0.09	59681 (18.9)	43641 (19.2)	-0.01
Obesity-related drugs	61 (0.0)	12 (0.0)	0.01	61 (0.0)	31 (0.0)	0.00
Antibiotics	190991 (60.4)	111208 (48.9)	0.23	190974 (60.4)	138744 (61.1)	-0.01
Contraceptives	40354 (12.8)	13461 (5.9)	0.24	40349 (12.8)	28532 (12.6)	0.01
Lab Tests Ordered:						
Glucose	21273 (6.7)	11049 (4.9)	0.08	21269 (6.7)	15704 (6.9)	-0.01
HbA1c	7946 (2.5)	4442 (2.0)	0.04	7945 (2.5)	5931 (2.6)	-0.01
Lipid	28716 (9.1)	17102 (7.5)	0.06	28712 (9.1)	21174 (9.3)	-0.01
Metabolic screening	85993 (27.2)	33855 (14.9)	0.31	85978 (27.2)	61293 (27.0)	0.00

Abbreviations: ADHD=Attention-deficit/hyperactivity disorder; ED=Emergency department; IQR=Interquartile range; NSAIDs=Nonsteroidal anti-inflammatory drugs; OCD=Obsessive-compulsive disorder; PTSD=Post-traumatic stress disorder; SSRIs=Selective serotonin reuptake inhibitors; std=Standard deviation; std diff=Standardized difference

Numbers reflect before considering first cohort entry.

^a Patients in the nonoverlapping regions of the propensity score distribution were trimmed. Within each propensity score decile, the bupropion patients were weighted using the distribution of the SSRI initiators.

eTable 9. Baseline Characteristics of Children and Adolescents With SSRI Compared With Psychotherapy Exposure in the IBM MarketScan ITT Population

	Unadjusted			Accounting for Propensity Score Decile ^a		
	No. (%) of patients		Std diff	No. (%) of patients		Std diff
	SSRIs	Psychotherapy		SSRIs	Psychotherapy	
No. of patients	221,460	249,781	-	221,459	249,774	-
Demographics:						
Age, years; mean (SD)	15.8 (2.3)	14.8 (2.3)	0.45	15.8 (2.3)	16.0 (2.2)	-0.08
Gender, female	135134 (63.9)	144899 (58.0)	0.12	135133 (63.9)	157502 (63.1)	0.02
Race/ethnicity						
White	N/A	N/A	N/A	N/A	N/A	N/A
Black	N/A	N/A	N/A	N/A	N/A	N/A
American Indian	N/A	N/A	N/A	N/A	N/A	N/A
Asian/Pacific Islander	N/A	N/A	N/A	N/A	N/A	N/A
Hispanic/Latino	N/A	N/A	N/A	N/A	N/A	N/A
Other	N/A	N/A	N/A	N/A	N/A	N/A
Year of index date						
2000-2005	15242 (7.2)	22823 (9.1)	-0.07	15242 (7.2)	18248 (7.3)	0.00
2006-2010	76600 (36.2)	102148 (40.9)	-0.10	76600 (36.2)	91601 (36.7)	-0.01
2011-2015	119618 (56.6)	124810 (50.0)	0.13	119617 (56.6)	139925 (56.0)	0.01
Healthcare utilization:						
No. of distinct generic drugs; median (IQR)	3 (1-5)	2 (0-4)	0.44	3 (1-5)	3 (1-6)	-0.07
No. of outpatient visits; median (IQR)	8 (4-14)	6 (4-9)	0.50	8 (4-14)	8 (5-12)	0.14
No. of mental health outpatient visits; median (IQR)	2 (0-5)	2 (2-2)	0.38	2 (1-6)	2 (2-3)	0.08
Hospitalization	18835 (8.9)	7911 (3.2)	0.20	18835 (8.9)	27599 (11.0)	-0.08
Mental health hospitalization	16229 (7.7)	5118 (2.1)	0.21	16229 (7.7)	24280 (9.7)	-0.08
ED visit	60925 (28.8)	54300 (21.7)	0.16	60925 (28.8)	79033 (31.6)	-0.06
Nutritionist visit	3008 (1.4)	3318 (1.3)	0.01	3008 (1.4)	3134 (1.3)	0.01
SSRI indications:						
Depression	155341 (73.5)	180016 (72.1)	0.03	155341 (73.5)	180634 (72.3)	0.03
OCD	11908 (5.6)	4451 (1.8)	0.20	11908 (5.6)	14706 (5.9)	-0.01
PTSD	6784 (3.2)	6906 (2.8)	0.03	6784 (3.2)	7611 (3.0)	0.01
Social anxiety disorder	6125 (2.9)	3074 (1.2)	0.12	6125 (2.9)	6700 (2.7)	0.01
Generalized anxiety disorder	109745 (51.9)	84178 (33.7)	0.21	109744 (51.9)	129786 (52.0)	-0.02
Panic disorder	12662 (6.0)	4952 (2.0)	0.37	12662 (6.0)	16069 (6.4)	0.00
Bulimia nervosa	2208 (1.0)	1401 (0.6)	0.05	2208 (1.0)	2274 (0.9)	0.01
Psychiatric conditions:						
ADHD	31850 (15.1)	24435 (9.8)	0.16	31849 (15.1)	39633 (15.9)	-0.02
Bipolar disorder	15650 (7.4)	7522 (3.0)	0.20	15650 (7.4)	23321 (9.3)	-0.07
Schizophrenia	511 (0.2)	278 (0.1)	0.03	511 (0.2)	1035 (0.4)	-0.03
Psychosis	3877 (1.8)	2002 (0.8)	0.09	3877 (1.8)	6832 (2.7)	-0.06
Adjustment disorder	11632 (5.5)	12718 (5.1)	0.02	11631 (5.5)	11717 (4.7)	0.04
Intellectual disability	3724 (1.8)	1762 (0.7)	0.10	3724 (1.8)	5694 (2.3)	-0.04
Disruptive behavior disorder	10020 (4.7)	8051 (3.2)	0.08	10020 (4.7)	12330 (4.9)	-0.01
Learning disorders	2228 (1.1)	1959 (0.8)	0.03	2228 (1.1)	3973 (1.6)	-0.05
Eating disorders	4897 (2.3)	2918 (1.2)	0.09	4897 (2.3)	5136 (2.1)	0.02
Metabolic conditions:						
Obesity	4017 (1.9)	3645 (1.5)	0.03	4017 (1.9)	4785 (1.9)	0.00

	Unadjusted			Accounting for Propensity Score Decile ^a		
	No. (%) of patients		Std diff	No. (%) of patients		Std diff
	SSRIs	Psychotherapy		SSRIs	Psychotherapy	
Overweight	1290 (0.6)	1468 (0.6)	0.00	1290 (0.6)	1435 (0.6)	0.00
Underweight	641 (0.3)	447 (0.2)	0.03	641 (0.3)	927 (0.4)	-0.01
Bariatric surgery	<11 (0.0)	<11 (0.0)	0.00	<11 (0.0)	<11 (0.0)	0.00
Weight management	3000 (1.4)	3311 (1.3)	0.01	3000 (1.4)	3131 (1.3)	0.01
Hyperlipidemia	2479 (1.2)	2631 (1.1)	0.01	2479 (1.2)	3096 (1.2)	-0.01
Hypothyroidism	2963 (1.4)	2093 (0.8)	0.05	2963 (1.4)	3893 (1.6)	-0.01
Hypothyroid screening	40537 (19.2)	23780 (9.5)	0.28	40537 (19.2)	52488 (21.0)	-0.05
Insulin resistance/Metabolic syndrome	2026 (1.0)	2042 (0.8)	0.01	2026 (1.0)	2651 (1.1)	-0.01
Nutritional deficiency	2581 (1.2)	1518 (0.6)	0.06	2581 (1.2)	3168 (1.3)	0.00
Other conditions:						
Smoking	3017 (1.4)	1415 (0.6)	0.09	3017 (1.4)	4608 (1.8)	-0.03
Alcohol abuse or dependence	3225 (1.5)	2589 (1.0)	0.04	3225 (1.5)	4733 (1.9)	-0.03
Drug abuse or dependence	7603 (3.6)	5303 (2.1)	0.09	7603 (3.6)	11754 (4.7)	-0.06
Back and neck pain	27864 (13.2)	26033 (10.4)	0.09	27864 (13.2)	35336 (14.1)	-0.03
Musculoskeletal pain	19980 (9.4)	24277 (9.7)	-0.01	19980 (9.4)	23760 (9.5)	0.00
Hypertension	1622 (0.8)	1088 (0.4)	0.04	1622 (0.8)	2259 (0.9)	-0.02
Cardiovascular symptoms	21041 (10.0)	16000 (6.4)	0.13	21041 (10.0)	28133 (11.3)	-0.04
Menstrual disorders	14922 (7.1)	9971 (4.0)	0.13	14922 (7.1)	18757 (7.5)	-0.02
Polycystic ovarian syndrome	759 (0.4)	510 (0.2)	0.03	759 (0.4)	993 (0.4)	-0.01
Medications:						
Antipsychotics	10524 (5)	2914 (1.2)	0.22	10524 (5.0)	16393 (6.6)	-0.07
Stimulants	33066 (15.6)	22584 (9.0)	0.20	33066 (15.6)	41683 (16.7)	-0.03
Benzodiazepines	20097 (9.5)	4781 (1.9)	0.33	20097 (9.5)	26140 (10.5)	-0.03
Barbiturates	1471 (0.7)	635 (0.3)	0.06	1471 (0.7)	2025 (0.8)	-0.01
Other hypnotics	9412 (4.5)	3385 (1.4)	0.19	9412 (4.5)	12588 (5.0)	-0.03
Anticonvulsants	8286 (3.9)	4363 (1.7)	0.13	8286 (3.9)	13097 (5.2)	-0.06
Mood Stabilizers	7052 (3.3)	3527 (1.4)	0.13	7052 (3.3)	11949 (4.8)	-0.07
NSAIDs	23798 (11.3)	17421 (7.0)	0.15	23798 (11.3)	30719 (12.3)	-0.03
Opioids	44800 (21.2)	36223 (14.5)	0.18	44800 (21.2)	57037 (22.8)	-0.04
Oral corticosteroids	22717 (10.7)	19573 (7.8)	0.10	22717 (10.7)	28153 (11.3)	-0.02
Bronchodilator	27553 (13)	28521 (11.4)	0.05	27553 (13)	32676 (13.1)	0.00
Obesity-related drugs	65 (0.0)	34 (0.0)	0.01	65 (0.0)	130 (0.1)	-0.01
Antibiotics	125287 (59.2)	124042 (49.7)	0.19	125287 (59.2)	149736 (59.9)	-0.01
Contraceptives	41265 (19.5)	22270 (8.9)	0.31	41265 (19.5)	52308 (20.9)	-0.04
Lab Tests Ordered:						
Glucose	12750 (6.0)	10376 (4.2)	0.09	12750 (6.0)	16683 (6.7)	-0.03
HbA1c	4969 (2.3)	4157 (1.7)	0.05	4969 (2.3)	6451 (2.6)	-0.02
Lipid	23309 (11.0)	21933 (8.8)	0.08	23308 (11.0)	28388 (11.4)	-0.01
Metabolic screening	59735 (28.2)	39369 (15.8)	0.30	59735 (28.2)	77918 (31.2)	-0.06

Abbreviations: ADHD=Attention-deficit/hyperactivity disorder; ED=Emergency department; IQR=Interquartile range; NSAIDs=Nonsteroidal anti-inflammatory drugs; OCD=Obsessive-compulsive disorder; PTSD=Post-traumatic stress disorder; SSRIs=Selective serotonin reuptake inhibitors; std=Standard deviation; std diff=Standardized difference

Numbers reflect before considering first cohort entry. Counts less than 11 denoted as <11 to protect patient privacy. Race/ethnicity is not available in the MarketScan database.

^a Patients in the nonoverlapping regions of the propensity score distribution were trimmed. Within each propensity score decile, the bupropion patients were weighted using the distribution of the SSRI initiators.

eTable 10. Unadjusted Absolute Rate of Type 2 Diabetes Among Children and Adolescents With SSRI Exposure or in a Comparator Group (Untreated, Bupropion, Psychotherapy)

Exposure Group	MAX					MarketScan				
	No of patients	No of events	Person-years	Incidence rate, per 1,000 PY	Mean follow up (years)	No of patients	No of events	Person-years	Incidence rate, per 1,000 PY	Mean follow up (years)
<i>Intention-to-treat population:</i>										
SSRIs	316,178	1,760	73,166	2.41	2.8	211,460	290	447,649	0.65	2.4
No antidepressant exposure	632,356	2,175	1,304,962	1.67	2.6	422,920	413	765,078	0.54	2.2
Bupropion	35,476	227	93,225	2.43	3.1	14,371	30	33,655	0.89	2.5
Psychotherapy	227,247	638	527,996	1.21	2.8	249,781	245	603,740	0.41	2.7
<i>As-treated population:</i>										
SSRIs	439,205	573	432,574	1.32	1.0	269,762	143	300,441	0.48	1.1
No antidepressant exposure	878,410	1,856	1,592,628	1.17	1.8	539,524	372	898,390	0.41	1.7
Bupropion	59,615	58	47,223	1.23	0.8	24,577	12	17,452	0.69	0.7
Psychotherapy	305,426	566	562,323	1.01	1.8	322,655	194	616,396	0.31	1.9

Abbreviations: PY=person-years; SSRIs=Selective serotonin reuptake inhibitors

In the intention-to-treat population, numbers reflect before considering first cohort entry.

eTable 11. Hazard Ratios and 95% Confidence Intervals Comparing the Incidence of Type 2 Diabetes Between SSRI Exposed and Untreated Children and Adolescents: Different Levels of Adjustment

	SSRI EXPOSED			UNTREATED			Hazard ratio (95% CI)
	No. of patients	No. of events	Person-years	No. of patients	No. of events	Person-years	
<i>Medicaid Analytic eXtract:</i>							
<u>Intention-to-treat:</u>							
Unadjusted	281,832	1,523	657,713	619,422	2,117	1,281,915	1.39 (1.31-1.49)
Partially adjusted	281,825	1,523	657,713	619,421	2,117	1,281,915	1.28 (1.18-1.37)
Fully adjusted	281,831	1,523	657,713	619,334	2,117	1,281,915	1.13 (1.04-1.22)
<u>As-treated:</u>							
Unadjusted	439,205	573	432,574	878,410	1,856	1,592,628	1.60 (1.47-1.74)
Baseline adjusted	439,205	573	432,574	878,410	1,856	1,592,628	1.39 (1.27-1.53)
Baseline & time-varying adjusted	439,205	573	432,574	878,410	1,856	1,592,628	1.33 (1.21-1.47)
<i>MarketScan:</i>							
<u>Intention-to-treat:</u>							
Unadjusted	181,947	245	391,733	415,670	406	752,732	1.16 (0.99-1.36)
Partially adjusted	181,947	245	391,733	415,670	406	752,732	1.04 (0.88-1.24)
Fully adjusted	181,947	245	391,733	415,670	406	752,732	1.01 (0.84-1.23)
<u>As-treated:</u>							
Unadjusted	269,762	143	300,441	539,524	372	898,390	1.18 (0.97-1.43)
Baseline adjusted	269,762	143	300,441	539,524	372	898,390	1.14 (0.92-1.41)
Baseline & time-varying adjusted	269,762	143	300,441	539,524	372	898,390	1.10 (0.88-1.36)

In the intention-to-treat analysis, partially adjusted accounts for demographics (age, sex, race for Medicaid only) and treatment indication and fully adjusted accounts for all baseline covariates. In the intention-to-treat analysis, only the first cohort entry was considered.

In the as-treated analysis, baseline adjusted accounts for all baseline covariates and baseline & time-varying adjusted accounts for all baseline and time-varying covariates.

eTable 12. Adjusted Risk Differences Comparing the Incidence of Type 2 Diabetes Between SSRI-Exposed and Untreated Children and Adolescents at 2 and 5 Years of Follow-up

	No. remaining in risk set		Adjusted risk difference, per 10,000	95% CI
	SSRI EXPOSED	UNTREATED		
MAX:				
<u>Intention-to-treat:</u>				
2 years	126,316	243,930	8.8	(5.1, 12.7)
5 years	30,890	56,676	25.8	(17.7, 37.5)
<u>As-treated:</u>				
2 years	127,561	535,617	6.6	(4.2, 10.4)
5 years	2,353	59,329	28.4	(16.0, 46.3)
MarketScan:				
<u>Intention-to-treat:</u>				
2 years	76,601	142,581	0.9	(-1.8, 3.2)
5 years	17,711	30,020	3.9	(-2.6, 9.5)
<u>As-treated:</u>				
2 years	93,468	294,879	0.4	(-1.9, 2.4)
5 years	269	29,688	3.7	(-3.2, 15.5)

Survival probabilities were estimated based on parameter estimates from pooled logistic marginal structural models (MSMs) and standardized to the joint-distribution of baseline covariates.^{2,3} In intention-to-treat analyses, MSMs were weighted by stabilized treatment weights based on baseline covariates. In as-treated analyses, MSMs were weighted by stabilized treatment and censoring weights based on baseline and time-varying covariates. Weights were truncated at the 1st and 99th percentiles to prevent outliers from affecting the analysis. 95% CIs for risk differences were estimated using nonparametric bootstrapping with 200 samples.

eTable 13. Hazard Ratios and 95% CIs Comparing the Incidence of Type 2 Diabetes Between SSRI- and Bupropion-Exposed Children and Adolescents: Different Levels of Adjustment

	SSRI EXPOSED			BUPROPION			Hazard ratio (95% CI)	
	No. of patients	No. of events	Person-years	No. of patients	No. of events	Person-years		
Medicaid Analytic eXtract:								
Intention-to-treat:								
Unadjusted	315,539	1,753	730,268	34,584	225	91,284	0.98 (0.86-1.13)	
Partially adjusted	315,539	1,753	730,268	34,584	225	91,284	0.85 (0.75-0.98)	
Fully adjusted	315,539	1,753	730,268	34,584	225	91,284	0.86 (0.75-0.99)	
As-treated:								
Unadjusted	439,205	573	432,574	59,615	58	47,223	0.93 (0.75-1.16)	
Baseline adjusted	439,205	573	432,574	59,615	58	47,223	1.06 (0.83-1.35)	
Baseline & time-varying adjusted	439,205	573	432,574	59,615	58	47,223	1.01 (0.79-1.29)	
MarketScan:								
Intention-to-treat:								
Unadjusted	211,257	289	535,822	14,041	29	37,932	0.70 (0.48-1.03)	
Partially adjusted	211,257	289	535,822	14,041	29	37,932	0.66 (0.45-0.95)	
Fully adjusted	211,257	289	535,822	14,041	29	37,932	0.76 (0.50-1.14)	
As-treated:								
Unadjusted	269,762	143	300,441	24,577	12	17,452	0.69 (0.38-1.25)	
Baseline adjusted	269,762	143	300,441	24,577	12	17,452	0.83 (0.43-1.62)	
Baseline & time-varying adjusted	269,762	143	300,441	24,577	12	17,452	0.87 (0.44-1.70)	

In the intention-to-treat analysis, partially adjusted accounts for demographics (age, sex, race for Medicaid only) and treatment indication and fully adjusted accounts for all baseline covariates. In the intention-to-treat analysis, only the first cohort entry was considered.

In the as-treated analysis, baseline adjusted accounts for all baseline covariates and baseline & time-varying adjusted accounts for all baseline and time-varying covariates.

eTable 14. Hazard Ratios and 95% CIs Comparing the Incidence of Type 2 Diabetes Between SSRI- and Psychotherapy-Exposed Children and Adolescents: Different Levels of Adjustment

	SSRI EXPOSED			PSYCHOTHERAPY			Hazard ratio (95% CI)	
	No. of patients	No. of events	Person-years	No. of patients	No. of events	Person-years		
Medicaid Analytic eXtract:								
<u>Intention-to-treat:</u>								
Unadjusted	301,801	1,677	701,514	226,419	634	526,280	1.96 (1.79-2.15)	
Partially adjusted	301,801	1,677	701,514	226,419	634	526,280	1.85 (1.69-2.04)	
Fully adjusted	301,801	1,677	701,514	226,419	634	526,280	1.45 (1.34-1.58)	
<u>As-treated:</u>								
Unadjusted	439,205	573	432,574	305,426	566	562,323	1.92 (1.72-2.15)	
Baseline adjusted	439,205	573	432,574	305,426	566	562,323	1.35 (1.14-1.60)	
Baseline & time-varying adjusted	439,205	573	432,574	305,426	566	562,323	1.44 (1.25-1.65)	
MarketScan:								
<u>Intention-to-treat:</u>								
Unadjusted	192,765	265	408,345	249,554	245	603,270	1.61 (1.35-1.92)	
Partially adjusted	192,765	265	408,345	249,554	245	603,270	1.43 (1.21-1.70)	
Fully adjusted	192,765	265	408,345	249,554	245	603,270	1.03 (0.88-1.21)	
<u>As-treated:</u>								
Unadjusted	269,762	143	300,441	322,655	194	616,396	1.53 (1.22-1.92)	
Baseline adjusted	269,762	143	300,441	322,655	194	616,396	1.19 (0.92-1.54)	
Baseline & time-varying adjusted	269,762	143	300,441	322,655	194	616,396	1.21 (0.93-1.57)	

In the intention-to-treat analysis, partially adjusted accounts for demographics (age, sex, race for Medicaid only) and treatment indication and fully adjusted accounts for all baseline covariates. In the intention-to-treat analysis, only the first cohort entry was considered.

In the as-treated analysis, baseline adjusted accounts for all baseline covariates and baseline & time-varying adjusted accounts for all baseline and time-varying covariates.

eTable 15. Hazard Ratios and 95% CIs Comparing the Incidence of Type 2 Diabetes Within the SSRI Class vs Fluoxetine

	No. of patients	No. of events	Person-years	Crude HR (95% CI)	Adjusted HR (95% CI)
Medicaid Analytic eXtract:					
Citalopram	44,331	239	93,099	2.57	1.04 (0.89-1.21)
Escitalopram	39,236	235	89,737	2.62	1.08 (0.92-1.26)
Fluvoxamine	1,349	12	4,505	2.66	1.00 (0.56-1.78)
Paroxetine	29,124	155	78,262	1.98	0.77 (0.64-0.92)
Sertraline	94,712	514	227,451	2.26	0.90 (0.79-1.02)
Fluoxetine	82,879	464	187,247	2.48	ref
MarketScan:					
Citalopram	30,152	46	62,420	1.22 (0.84-1.78)	1.27 (0.87-1.85)
Escitalopram	38,634	40	78,919	0.85 (0.57-1.25)	0.91 (0.61-1.35)
Fluvoxamine	1,113	<11 ^a	2,783	0.61 (0.09-4.40)	0.66 (0.09-4.75)
Paroxetine	8,639	11	19,796	0.93 (0.49-1.76)	1.17 (0.62-2.23)
Sertraline	64,537	90	136,058	1.11 (0.81-1.52)	1.22 (0.88-1.69)
Fluoxetine	52,774	68	113,885	ref	ref

^aTo protect patient privacy, counts of less than 11 are denoted as “<11”.

eTable 16. Hazard Ratios and 95% CIs Comparing the Incidence of Type 2 Diabetes Between SSRI-Exposed and Untreated Children and Adolescents: Subgroup Analyses in ITT Population

	SSRI EXPOSED			UNTREATED			Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
	No. of patients	No. of events	Person-years	No. of patients	No. of events	Person-years		
MAX:								
<i>Age:</i>								
10-14 years	135,465	873	296,016	292,881	1,201	761,205	1.39 (1.28-1.52)	1.08 (0.99-1.17)
15-19 years	146,367	650	261,697	326,541	916	520,711	1.39 (1.26-1.54)	1.18 (1.07-1.30)
<i>Gender:</i>								
Female	174,971	1,094	382,475	338,095	1,426	650,671	1.30 (1.20-1.40)	1.08 (1.01-1.17)
Male	106,851	429	275,208	281,319	689	630,816	1.40 (1.24-1.58)	1.24 (1.11-1.40)
<i>Race:</i>								
White	175,012	767	391,296	290,720	869	588,389	1.32 (1.20-1.46)	1.08 (0.98-1.19)
Black	44,717	390	117,798	147,413	617	317,308	1.70 (1.50-1.93)	1.24 (1.11-1.40)
Hispanic/Latino	39,302	207	91,396	121,579	368	245,330	1.50 (1.26-1.78)	1.19 (1.01-1.40)
Other	22,801	159	57,224	59,710	263	130,888	1.37 (1.13-1.67)	1.00 (0.83-1.21)
<i>Other:</i>								
Depression diagnosis	235,268	1,306	547,196	438,722	1,539	910,391	1.41 (1.31-1.51)	1.15 (1.08-1.24)
Anxiety diagnosis	91,186	402	194,871	174,155	558	344,183	1.27 (1.12-1.45)	0.95 (0.84-1.07)
No antipsychotic use	240,776	1,151	540,780	559,096	1,673	1,127,892	1.43 (1.33-1.54)	1.20 (1.12-1.29)
Stimulant use	54,641	364	149,309	99,212	483	244,487	1.23 (1.07-1.41)	1.08 (0.94-1.23)
MarketScan:								
<i>Age:</i>								
10-14 years	53,737	82	124,580	117,823	114	228,580	1.32 (0.99-1.75)	0.98 (0.75-1.29)
15-19 years	128,210	163	267,153	297,847	292	524,152	1.10 (0.91-1.33)	1.03 (0.85-1.25)
<i>Gender:</i>								
Female	115,232	195	243,500	240,228	304	422,477	1.11 (0.93-1.33)	0.99 (0.83-1.18)
Male	66,715	50	148,233	175,442	102	330,255	1.10 (0.78-1.54)	1.05 (0.75-1.47)
<i>Other:</i>								
Depression diagnosis	132,666	194	286,648	263,104	294	490,324	1.13 (0.95-1.36)	0.98 (0.82-1.18)
Anxiety diagnosis	94,157	110	187,103	173,308	141	287,972	1.20 (0.94-1.54)	0.99 (0.78-1.26)
No antipsychotic use	173,144	221	372,407	402,501	368	729,974	1.18 (1.00-1.39)	1.04 (0.88-1.22)
Stimulant use	27,707	36	59,813	57,950	65	104,215	0.96 (0.64-1.45)	0.90 (0.60-1.34)

Abbreviations: MAX=Medicaid Analytic eXtract

Subgroups defined based on baseline patient characteristics, measured during the 365 days prior to index date. Race data is not available in MarketScan.

eTable 17. Hazard Ratios and 95% CIs Comparing the Incidence of Type 2 Diabetes Between SSRI-Exposed and Untreated Children and Adolescents: Sensitivity Analyses in ITT Population

	SSRI EXPOSED			UNTREATED			Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
	No. of patients	No. of events	Person-years	No. of patients	No. of events	Person-years		
MAX:								
No 2+ exposure requirement ^a	342,394	1,693	954,008	852,614	2,927	2,159,691	1.27 (1.20-1.35)	1.07 (1.01-1.13)
HdPS ^b	281,832	1,523	657,713	619,422	2,117	1,281,915	1.39 (1.31-1.49)	1.14 (1.07-1.22)
<i>Control outcomes:</i> ^c								
Asthma	237,352	21,465	514,473	532,027	39,456	1,037,075	1.11 (1.09-1.13)	0.97 (0.95-0.99)
Hyperlipidemia	277,855	5,303	641,551	610,443	9,158	1,253,680	1.12 (1.08-1.16)	0.96 (0.92-1.00)
<i>MarketScan:</i>								
No 2+ exposure requirement	198,313	259	530,469	527,035	517	1,214,330	1.10 (0.95-1.28)	0.99 (0.86-1.15)
HdPS	181,947	245	391,733	415,670	406	752,732	1.16 (0.99-1.36)	1.08 (0.92-1.27)
<i>Control outcomes:</i>								
Asthma	163,995	7,247	340,931	373,442	13,850	657,460	1.03 (1.00-1.06)	0.97 (0.94-1.01)
Hyperlipidemia	179,602	1,910	383,878	409,369	3,959	737,364	0.92 (0.87-0.97)	0.83 (0.78-0.88)

Abbreviations: HdPS=high dimensional propensity score; IP=inverse probability; MAX=Medicaid Analytic eXtract; PS=propensity score

^aNo exposure requirements during the 180 days post index date (ex: 2+ dispensings not required), consider first cohort entry only, follow up began on index date.

^bHdPS analyses included 200 empirically defined covariates, in addition to all pre-specified baseline covariates.

^c Hyperlipidemia and asthma were selected *a priori* based on subject matter knowledge as outcomes that should have no association with SSRIs, but may have a similar structure of confounding or similar potential for detection bias as type 2 diabetes. A null association between SSRIs and control outcomes would provide indirect evidence of no substantial residual confounding or detection bias.⁴ In negative control analyses, patients with a diagnosis of the control outcome during the 365 days prior to index date were excluded. Similar to the primary analysis, the first cohort entry was considered and patients with the outcome during the first 180 days after index date were excluded. Asthma cases were defined as having 1) ≥2 asthma diagnoses codes (ICD-9-CM diagnosis code 493.xx) within 1 year of each other, 2) ≥1 inpatient asthma diagnosis, or 3) ≥1 asthma diagnosis and ≥1 asthma medication prescription. Hyperlipidemia cases were defined similarly based on diagnosis for hyperlipidemia (ICD-9-CM diagnosis code 272.xx) and lipid-lowering medication prescriptions. These criteria mimicked the criteria for type 2 diabetes to approximate the intensity of outcome surveillance.

eTable 18. Hazard Ratios and 95% CIs Comparing the Incidence of Type 2 Diabetes Between SSRI-Exposed and Untreated Children and Adolescents: Sensitivity Analyses in As-Treated Population

	Medicaid Analytic eXtract		IBM MarketScan	
	Mean (std) of weights ^a	Adjusted hazard ratio (95% CI)	Mean (std) of weights	Adjusted hazard ratio (95% CI)
Percentiles of truncation:				
0.1, 99.9	0.99 (0.42)	1.33 (1.21-1.47)	1.01 (0.32)	1.10 (0.88-1.36)
0.5, 99.5	0.99 (0.35)	1.33 (1.21-1.47)	1.02 (0.45)	1.07 (0.86-1.30)
1.0, 99.0 (Primary analysis)	0.98 (0.32)	1.33 (1.21-1.47)	1.02 (0.35)	1.10 (0.88-1.37)
2.0, 98.0	0.97 (0.28)	1.33 (1.21-1.47)	1.00 (0.28)	1.09 (0.88-1.36)
Censoring model:				
Separated by censorship reason (Primary analysis)	0.99 (0.42)	1.33 (1.21-1.47)	1.02 (0.35)	1.10 (0.88-1.37)
Combined model ^b	0.98 (0.28)	1.30 (1.18-1.43)	1.02 (0.30)	1.11 (0.89-1.38)

^aTo estimate valid treatment effect estimates, mean of the weights should be approximately 1.00.

^bIn the primary analysis, weight models for censoring were estimated separately for treatment-related censoring (treatment discontinuation, treatment switching) and study-related censoring to allow better prediction of these different types of censorship events.⁵ The combined model fits one single model for all censorship events.

eTable 19. Flowchart of the Claims Electronic Health Records–Linked Study Population (Medicaid Analytic eXtract Claims Linked to the Partners Healthcare Research Patient Data Registry)

Step	Remaining Patients	% Excluded
Medicaid Analytic eXtract study cohort – Massachusetts (includes SSRI exposed and all comparator groups)	20,740	-
Linked to Partners Healthcare Research Patient Data Registry (electronic health records)	2,387	88.5%
Presence of any body mass index (BMI) data	896	62.5%
Presence of any BMI data prior to index date	483	46.1%
Presence of BMI data during the 365 days prior to index date (covariate assessment period) ^a	300	37.9%
Final cohort:	SSRI: 73 Untreated: 160 Bupropion: 8 Psychotherapy: 59	-

^a For patients with multiple BMI measurements during the covariate assessment period, the most recent measurement was used.

eTable 20. Patient Characteristics And Body Mass Index Data For Children And Adolescents With SSRI Exposure And Without Antidepressant Exposure In The Claims Electronic Health Records (MAX-RPDR)–Linked Subset

	Unadjusted			Propensity Score Weighted ^a		
	No. (%) of patients		Std diff	No. (%) of patients		Std diff
	SSRIs	Untreated		SSRIs	Untreated	
No. of patients	73	160	-	80	156	-
EHR data (RPDR):						
BMI; mean (std)	24.61 (8.5)	25.10 (7.5)	-0.06	25.56 (8.7)	25.22 (7.6)	0.04
BMI categories						
Underweight (<18.5)	14 (19.2)	17 (10.6)	0.24	14 (17.8)	17 (11.1)	0.19
Normal weight (18.5-24.9)	30 (41.1)	71 (44.4)	-0.07	27 (33.9)	67 (42.7)	-0.18
Overweight (25-29.9)	16 (21.9)	39 (24.4)	-0.06	19 (23.3)	38 (24.1)	-0.02
Obesity (>30)	13 (17.8)	33 (20.6)	-0.07	20 (24.9)	35 (22.1)	0.07
Claims data (MAX):						
<u>Demographics:</u>						
Age (years); mean (std)	14.47 (2.1)	14.88 (2.3)	-0.19	14.80 (2.2)	14.76 (2.2)	0.02
Gender, female	46 (63.0)	77 (48.1)	0.30	35 (44.0)	80 (50.9)	-0.14
Race, white	41 (56.2)	72 (45)	0.22	37 (46.6)	75 (47.7)	-0.02
<u>Healthcare Utilization:</u>						
No. of distinct generic drugs, excluding AD; median (IQR)	4 (2-7)	5 (2-8)	0.00	4 (2-8)	5 (2-8)	0.10
No. of outpatient visits; median (IQR)	26 (19-49)	35 (23-57)	-0.11	30 (17-71)	35 (23-56)	0.09
No. of mental-health outpatient visits; median (IQR)	1 (0-14)	3 (0-21)	-0.03	1 (0-16)	3 (0-22)	0.04
<u>Medications:</u>						
Antipsychotics	5 (6.8)	32 (20.0)	-0.39	18 (22.7)	26 (16.3)	0.16
Stimulants	21 (28.8)	40 (25.0)	0.09	22 (27.4)	36 (23.2)	0.10
Benzodiazepines	6 (8.2)	7 (4.4)	0.16	5 (6.1)	6 (4.0)	0.10
Anticonvulsants	3 (4.1)	24 (15.0)	-0.38	11 (13.6)	19 (12.0)	0.05
Mood Stabilizers	3 (4.1)	21 (13.1)	-0.33	11 (13.6)	17 (10.8)	0.08
NSAIDs	19 (26.0)	37 (23.1)	0.07	26 (32.4)	40 (25.4)	0.15
Opioids	7 (9.6)	17 (10.6)	-0.03	10 (12.3)	16 (10.4)	0.06
<u>Medical Diagnoses:</u>						
Depression	57 (78.1)	94 (58.8)	0.43	47 (58.1)	100 (63.8)	-0.12
OCD	0 (0.0)	3 (1.9)	-0.20	0 (0.0)	2 (1.4)	-0.17
PTSD	11 (15.1)	29 (18.1)	-0.08	18 (22.0)	32 (20.3)	0.04
Social anxiety disorder	0 (0.0)	1 (0.6)	-0.11	0 (0.0)	1 (0.5)	-0.10
Panic disorder	1 (1.4)	5 (3.1)	-0.12	1 (1.6)	5 (3.0)	-0.10
Generalized anxiety disorder	30 (41.1)	77 (48.1)	-0.14	33 (41.6)	73 (46.2)	-0.09
Bulimia nervosa	1 (1.4)	0 (0.0)	0.17	0 (0.6)	0 (0.0)	0.11
Psychotherapy	16 (21.9)	35 (29.2)	-0.17	20 (24.6)	39 (32.5)	-0.18
ADHD	18 (24.7)	35 (21.9)	0.07	24 (29.5)	33 (21.3)	0.19
Bipolar disorder	22 (30.1)	31 (19.4)	0.25	16 (19.8)	33 (21.2)	-0.04
Smoking	0 (0.0)	1 (0.6)	-0.11	0 (0.0)	1 (0.6)	-0.11
Drug abuse or dependence	7 (9.6)	10 (6.3)	0.12	4 (5.5)	8 (5.4)	0.00
Obesity	7 (9.6)	13 (8.1)	0.05	9 (10.6)	14 (8.7)	0.06
Underweight	1 (1.4)	4 (2.5)	-0.08	1 (1.6)	3 (2.2)	-0.04

Abbreviations: AD=Antidepressants; ADHD=Attention-deficit/hyperactivity disorder; BMI=Body mass index; IQR=Interquartile range; MAX=Medicaid Analytic eXtract; OCD=Obsessive-compulsive disorder; PTSD=Post-traumatic stress disorder; RPDR=Partners Healthcare Research Patient Data Registry; SSRIs=Selective serotonin reuptake inhibitors; std=Standard deviation; std diff=Standardized difference.

^aWeighted by the inverse of the propensity score. The propensity score model included age, gender, race, depression, antipsychotics, anticonvulsants, mood stabilizers, obesity, underweight, bipolar disorder.

eTable 21. Patient Characteristics and Body Mass Index Data for Children and Adolescents With SSRI and Bupropion Exposure in the Claims Electronic Health Records (MAX-RPDR)-Linked Subset

	Unadjusted		
	No. (%) of patients		Std diff
	SSRIs	Bupropion	
No. of patients	73	8	-
EHR data (RPDR):			
BMI; mean (std)	24.61 (8.5)	25.01 (7.8)	-0.05
BMI categories			
Underweight (<18.5)	14 (19.2)	2 (25.0)	-0.14
Normal weight (18.5-24.9)	30 (41.1)	2 (25.0)	0.35
Overweight (25-29.9)	16 (21.9)	2 (25.0)	-0.07
Obesity (>30)	13 (17.8)	2 (25.0)	-0.18
Claims data (MAX):			
<u>Demographics:</u>			
Age (years); mean (std)	14.47 (2.1)	15.25 (1.9)	-0.39
Gender, female	46 (63.0)	4 (50.0)	0.26
Race, white	41 (56.2)	2 (25.0)	0.67
<u>Healthcare Utilization:</u>			
No. of distinct generic drugs, excluding AD; median (IQR)	4 (2-7)	6 (3-10)	-0.31
No. of outpatient visits; median (IQR)	26 (19-49)	23 (18-52)	0.28
No. of mental-health outpatient visits; median (IQR)	1 (0-14)	2 (0-30)	0.08
<u>Medications:</u>			
Antipsychotics	5 (6.8)	5 (62.5)	-1.44
Stimulants	21 (28.8)	6 (75.0)	-1.04
Benzodiazepines	6 (8.2)	0 (0.0)	0.42
Anticonvulsants	3 (4.1)	4 (50.0)	-1.21
Mood Stabilizers	3 (4.1)	4 (50.0)	-1.21
NSAIDs	19 (26.0)	3 (37.5)	-0.25
Opioids	7 (9.6)	1 (12.5)	-0.09
<u>Medical Diagnoses:</u>			
Depression	57 (78.1)	4 (50.0)	0.61
OCD	0 (0.0)	0 (0.0)	0.00
PTSD	11 (15.1)	0 (0.0)	0.60
Social anxiety disorder	0 (0.0)	0 (0.0)	0.00
Panic disorder	1 (1.4)	1 (12.5)	-0.45
Generalized anxiety disorder	30 (41.1)	4 (50.0)	-0.18
Bulimia nervosa	1 (1.4)	0 (0.0)	0.17
Psychotherapy	16 (21.9)	2 (25.0)	-0.07
ADHD	18 (24.7)	3 (37.5)	-0.28
Bipolar disorder	22 (30.1)	4 (50.0)	-0.41
Smoking	0 (0.0)	0 (0.0)	0.00
Drug abuse or dependence	7 (9.6)	1 (12.5)	-0.09
Obesity	7 (9.6)	3 (37.5)	-0.70
Underweight	1 (1.4)	0 (0.0)	0.17

Abbreviations: AD=Antidepressants; ADHD=Attention-deficit/hyperactivity disorder; BMI=Body mass index; IQR=Interquartile range; MAX=Medicaid Analytic eXtract; OCD=Obsessive-compulsive disorder; PTSD=Post-traumatic stress disorder; RPDR=Partners Healthcare Research Patient Data Registry; SSRIs=Selective serotonin reuptake inhibitors; std=Standard deviation; std diff=Standardized difference
Propensity score weighting not conducted due to small number of bupropion users.

eTable 22. Patient Characteristics and Body Mass Index Data for Children and Adolescents With SSRI and Psychotherapy Exposure in the Claims Electronic Health Records (MAX-RPDR)-Linked Subset

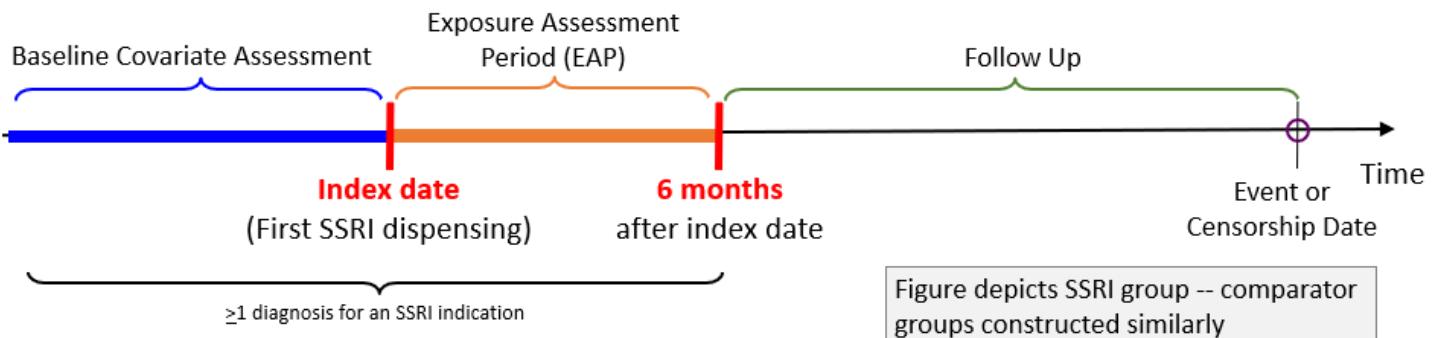
	Unadjusted			Propensity Score Weighted ^a		
	No. (%) of patients		Std diff	No. (%) of patients		Std diff
	SSRIs	Psychotherapy		SSRIs	Psychotherapy	
No. of patients	73	59	-	73	57	-
EHR data (RPDR):						
BMI; mean (std)	24.61 (8.5)	25.01 (9.3)	-0.05	25.61 (8.8)	25.91 (9.2)	-0.03
BMI categories						
Underweight (<18.5)	14 (19.2)	10 (16.9)	0.06	12 (16.1)	9 (15.1)	0.03
Normal weight (18.5-24.9)	30 (41.1)	28 (47.5)	-0.13	26 (36.3)	24 (41.6)	-0.11
Overweight (25-29.9)	16 (21.9)	11 (18.6)	0.08	17 (24.0)	14 (24.0)	0.00
Obesity (>30)	13 (17.8)	10 (16.9)	0.02	17 (23.6)	11 (19.3)	0.11
Claims data (MAX):						
Demographics:						
Age (years); mean (std)	14.47 (2.1)	14.12 (2.2)	0.16	14.39 (2.1)	14.53 (2.2)	-0.07
Gender, female	46 (63.0)	30 (50.8)	0.25	41 (56.7)	31 (54.8)	0.04
Race, white	41 (56.2)	17 (28.8)	0.58	32 (44.4)	24 (41.2)	0.06
Healthcare Utilization:						
No. of distinct generic drugs, excluding AD; median (IQR)	4 (2-7)	3 (1-6)	0.21	4 (2-7)	4 (2-6)	0.12
No. of outpatient visits; median (IQR)	26 (19-49)	25 (20-45)	0.26	26 (19-49)	27 (21-35)	0.31
No. of mental-health outpatient visits; median (IQR)	1 (0-14)	2 (1-5)	0.36	1 (0-14)	2 (-15)	0.36
Medications:						
Antipsychotics	5 (6.8)	4 (6.8)	0.00	5 (7.5)	4 (7.4)	0.00
Stimulants	21 (28.8)	11 (18.6)	0.24	18 (24.2)	12 (21.5)	0.06
Benzodiazepines	6 (8.2)	1 (1.7)	0.30	4 (5.2)	1 (2.5)	0.14
Anticonvulsants	3 (4.1)	3 (5.1)	-0.05	4 (6.1)	4 (6.1)	0.00
Mood Stabilizers	3 (4.1)	4 (6.8)	-0.12	4 (6.1)	4 (7.3)	-0.05
NSAIDs	19 (26.0)	11 (18.6)	0.18	22 (29.8)	14 (24.1)	0.13
Opioids	7 (9.6)	5 (8.5)	0.04	9 (12.6)	8 (14.8)	-0.07
Medical Diagnoses:						
Depression	57 (78.1)	38 (64.4)	0.31	54 (73.8)	41 (71.5)	0.05
OCD	0 (0.0)	0 (0.0)	0.00	0 (0.0)	0 (0.0)	0.00
PTSD	11 (15.1)	13 (22)	-0.18	11 (15.2)	13 (22.1)	-0.18
Social anxiety disorder	0 (0.0)	1 (1.7)	-0.19	0 (0.0)	1 (2.5)	-0.22
Panic disorder	1 (1.4)	0 (0.0)	0.17	1 (1.2)	0 (0.0)	0.15
Generalized anxiety disorder	30 (41.1)	22 (37.3)	0.08	31 (42.4)	23 (39.3)	0.06
Bulimia nervosa	1 (1.4)	0 (0.0)	0.17	1 (1.0)	0 (0.0)	0.14
ADHD	18 (24.7)	9 (15.3)	0.24	16 (22.5)	9 (15.9)	0.17
Bipolar disorder	22 (30.1)	9 (15.3)	0.36	18 (24.4)	15 (25.6)	-0.03
Smoking	0 (0.0)	1 (1.7)	-0.19	0 (0.0)	1 (2.5)	-0.23
Drug abuse or dependence	7 (9.6)	3 (5.1)	0.17	5 (7.0)	6 (11.3)	-0.15
Obesity	7 (9.6)	9 (15.3)	-0.17	10 (13.4)	8 (13.9)	-0.01
Underweight	1 (1.4)	2 (3.4)	-0.13	1 (0.9)	1 (1.7)	-0.07

Abbreviations: AD=Antidepressants; ADHD=Attention-deficit/hyperactivity disorder; BMI=Body mass index; IQR=Interquartile range; MAX=Medicaid Analytic eXtract; OCD=Obsessive-compulsive disorder; PTSD=Post-traumatic stress disorder; RPDR=Partners Healthcare Research Patient Data Registry; SSRIs=Selective serotonin reuptake inhibitors; std=Standard deviation; std diff=Standardized difference

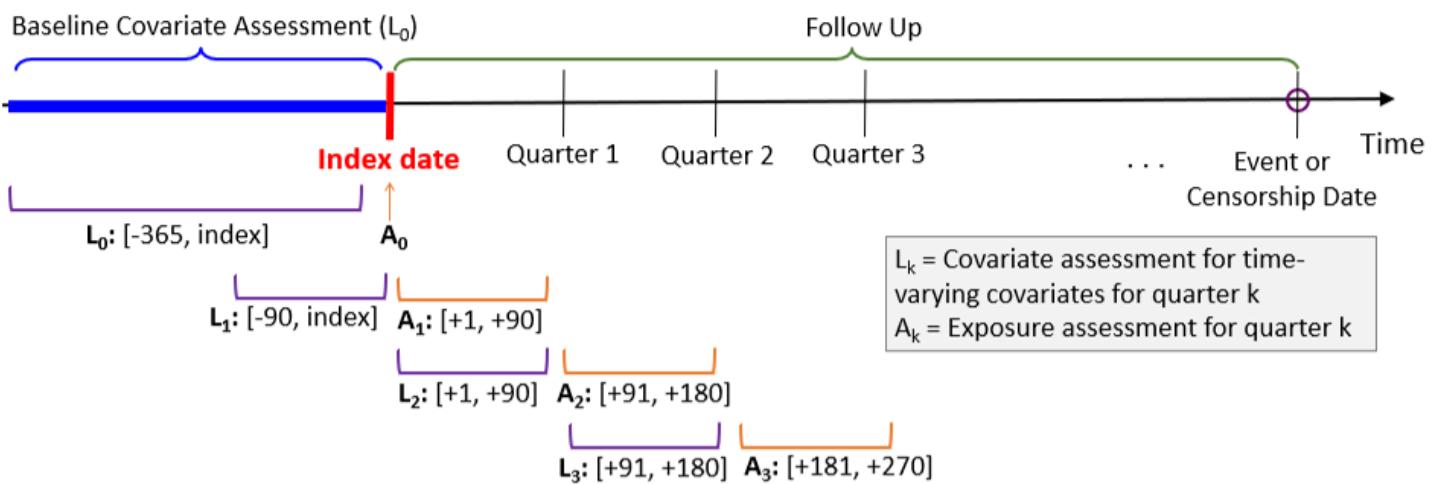
^aWeighted by the inverse of the propensity score. The propensity score model included age, gender, race, depression, mood stabilizers, obesity, underweight, bipolar disorder, stimulants, benzodiazepines.

eFigure 1. Study Design Diagrams for the ITT and As-Treated Analyses

Intention-to-treat analysis:



As-treated analysis:



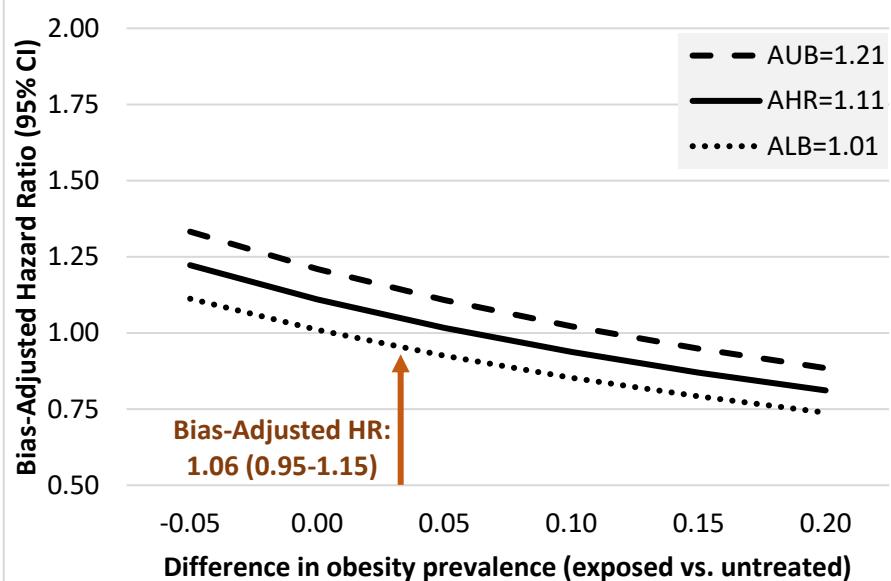
The ITT analysis was restricted to patients with at least 1 additional SSRI prescription during the 180 days after the index dispensing (exposure assessment period [EAP]). Untreated patients were required to have no antidepressant prescriptions and at least 1 additional medical encounter during the EAP. Bupropion initiators were required to have at least 1 additional bupropion prescription during the EAP. Psychotherapy initiators were required to have at least 1 additional psychotherapy code and have no antidepressant exposure during the EAP. Within class, patients were required to have at least 1 additional prescription of their index SSRI treatment.

By beginning follow up 180 days after index date, we are assuming that there is no effect during the first 6 months of treatment. Findings can be extrapolated to patients with at least 2 prescriptions during the first 180 days.

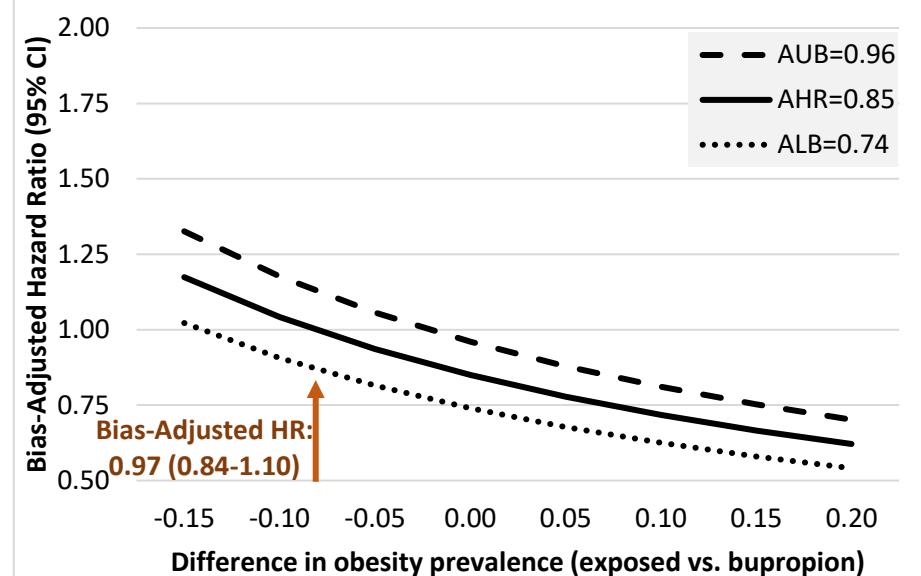
In the ITT analysis, for patients who appeared in both the exposed and comparator group, only first cohort entry was considered.

eFigure 2. Potential Role of Obesity as an Unmeasured Confounder on the Observed Hazard Ratios and 95% CIs in the ITT Population

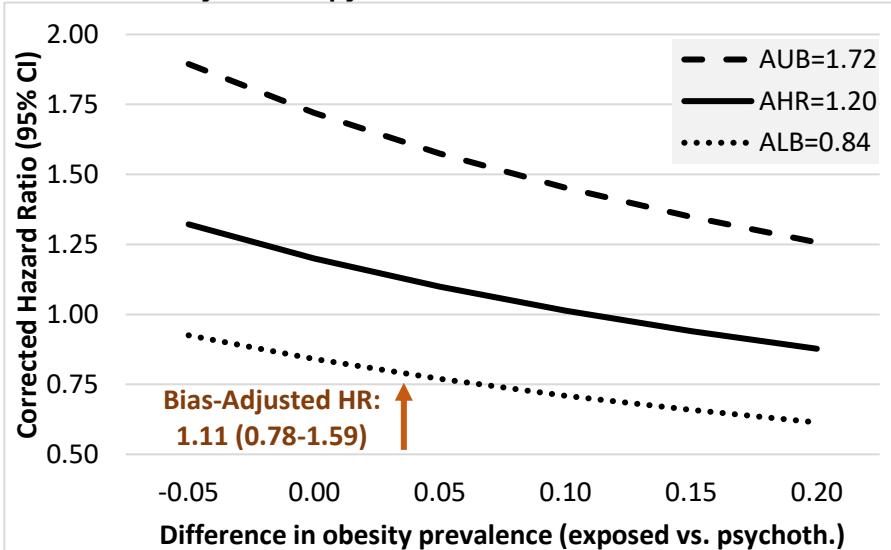
A. SSRIs vs. Untreated



B. SSRIs vs. Bupropion



C. SSRIs vs. Psychotherapy



Difference in obesity prevalence (x-axis) estimated as prevalence in exposed (P_{C1}) minus prevalence in untreated (P_{C0}). Untreated obesity prevalence was based on CDC estimates childhood & adolescent obesity in the US.⁸ Assuming that obese children and adolescents have 4 times the risk of type 2 diabetes compared to non-obese children and adolescents (RR_{CD}),⁹ corrected hazard ratios and 95% CIs (y-axis) were estimated by dividing the apparent hazard ratio (fully adjusted pooled hazard ratio observed in ITT analysis, using random effects meta-analysis to pool findings across databases) before adjustment for obesity by the following bias factor:⁶

$$\text{Bias factor} = \frac{P_{C1} (RR_{CD} - 1) + 1}{P_{C0} (RR_{CD} - 1) + 1}$$

The solid line corresponds to the point estimate, and dotted lines correspond to the upper and lower bounds of the 95% CI. The orange arrow shows the difference in obesity prevalence observed in Medicaid claims-electronic health records linked subset of our study population after propensity score weighting (crude for bupropion comparison due to small sample size) and corresponding bias-adjusted estimates.

eMethods. Quantification of the Potential Impact of Residual Confounding by Poorly Measured Obesity

Background: Obesity could be an important confounder of the association between SSRIs & type 2 diabetes (T2DM) because adolescents with more severe depression are more likely to be overweight/obese and to develop T2DM. However, it is poorly captured in administrative data. We explored the potential impact of residual confounding due to poorly measured obesity.

Methods: For a subset of the MAX population, body mass index (BMI) data was obtained by linking their claims data to the Partners Healthcare Research Patient Data Registry (RPDR), an electronic health record database comprised of patients who receive their care in the Partners hospital systems in Massachusetts. Information from this linked subset and the literature was used to inform bias analyses that investigate the potential impact of obesity as an unmeasured confounder on the observed point estimates and 95% CIs.⁶⁻⁹ Specifically, we used the bias factor developed by Bross and Schlesselman to estimate bias-adjusted hazard ratios and 95% CIs.^{6,7} Assuming that obese children and adolescents have 4 times the risk of T2DM compared to non-obese children and adolescents (RR_{CD}),⁹ bias-adjusted hazard ratios and 95% CIs were estimated by dividing the apparent hazard ratio (fully adjusted pooled hazard ratio observed in ITT analysis) before adjustment for obesity by the following bias factor:

$$\text{Bias factor} = \frac{P_{C1} (RR_{CD}-1) + 1}{P_{C0} (RR_{CD}-1) + 1}$$

Untreated obesity prevalence (P_{C0}) was based on Centers for Disease Control and Prevention (CDC)'s estimates of childhood & adolescent obesity in the US.⁸ Difference in obesity prevalence, defined as prevalence in exposed (P_{C1}) minus prevalence in untreated (P_{C0}), was further informed by numbers observed in claims-electronic health records linked subset of our study population.

Results: Medicaid claims were linked to electronic health records for 73 exposed and 160 untreated patients (**eTable19**). Within this subset of patients, overall BMI (mean, 25.56 vs. 25.22) and obesity prevalence (24.9% vs. 22.1%) were balanced across treatment groups (standardized difference<0.1) after accounting for select patient characteristics through propensity score weighting (**eTable20**). Bias analyses illustrated the potential role of unmeasured obesity on observed estimates across a range of prevalences (**eFigure2**). Assuming a 4-fold increased risk of T2DM among obese children and adolescents compared to nonobese patients,⁹ the pooled aHR could range from 0.81 (95% CI, 0.74-0.88) to 1.22 (95% CI, 1.11-1.33), assuming prevalence differences in exposed vs. untreated ranging from -0.05 to 0.20. Based on the difference in obesity prevalence observed in the linked subset, better captured obesity measurements would not have substantially altered our primary analysis (bias-adjusted pooled aHR, 1.06, 95% CI, 0.96-1.15) or the active comparator analyses (bias-adjusted pooled aHR, 0.97, 95% CI, 0.84-1.10 vs. bupropion; bias-adjusted pooled aHR, 1.11, 95% CI, 0.78-1.59 vs. psychotherapy). While we assumed that the relationship between obesity and T2DM was 4-fold higher among obese children and adolescents compared to nonobese patients, this is an extreme estimate, as adjustment for baseline covariates in claims data (including measured obesity) may have attenuated this relationship.

Conclusions: It is unlikely that better measurement of obesity would have substantially altered our findings.

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